

Nos. 2025-1236, -1241

United States Court of Appeals
for the Federal Circuit

EXELIXIS, INC.,
Plaintiff-Cross-Appellant

v.

MSN LABORATORIES PRIVATE LTD.,
MSN PHARMACEUTICALS, INC.
Defendants-Appellants

Appeal from the U.S. District Court for the District of Delaware,
Case No. 1:22-cv-00228-RGA, Judge Richard G. Andrews

PRINCIPAL BRIEF FOR DEFENDANTS-APPELLANTS

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CLAIM LANGUAGE

U.S. Patent No. 11,091,439, Claim 4 (Appx141)

1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, *wherein said salt is crystalline.*
3. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is the (L)-malate salt or (D)-malate salt.
4. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (L)-malate salt.

U.S. Patent No. 11,091,440, Claim 3 (Appx190)

3. A pharmaceutical composition comprising the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxylphenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or (D)-malate salt and *wherein said salt is crystalline*; and a pharmaceutically acceptable excipient.

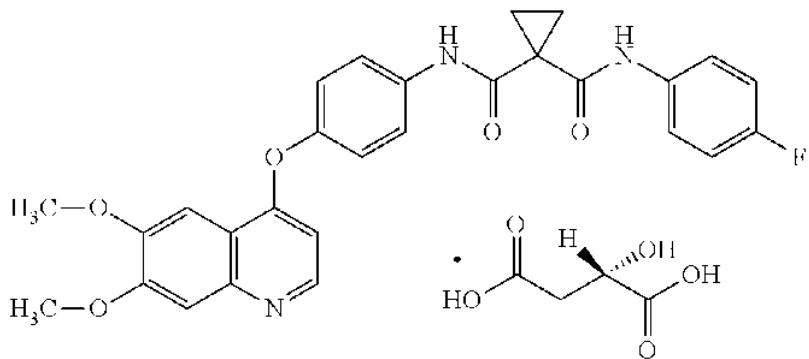
U.S. Patent No. 11,098,015, Claim 2 (Appx239)

2. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, *said salt is crystalline*, and said cancer is kidney cancer.

U.S. Patent No. 11,298,349, Claim 3 (Appx92)

1. A pharmaceutical composition for oral administration comprising Compound IB;

IB



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition; and

wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.

CERTIFICATE OF INTEREST

Undersigned counsel certifies that the following information is accurate and complete to the best of counsel's knowledge:

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	2. Real Party in Interest. Fed. Cir. R. 47.4(a)(2).	3. Parent Corporations and Stockholders. Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.
MSN Laboratories Private Ltd.	N/A	None
MSN Pharmaceuticals, Inc.	N/A	MSN Laboratories Private Ltd.

- 4. Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

Winston & Strawn LLP: George C. Lombardi, Elizabeth E. Grden, Brian L. O'Gara

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5. **Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

Yes

6. **Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

None/Not Applicable

/s/ Bryce A. Cooper
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April 1, 2025

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GLOSSARY OF ABBREVIATIONS

'015 patent	U.S. Patent No. 11,098,015 (Appx191-239)
'349 patent	U.S. Patent No. 11,298,349 (Appx73-92)
'439 patent	U.S. Patent No. 11,091,439 (Appx93-141)
'440 patent	U.S. Patent No. 11,091,440 (Appx142-190)
'473 patent	U.S. Patent No. 7,579,473 (Appx2843-3051)
'549 patent	U.S. Patent No. 9,809,549 (Appx10630-10676)
'776 patent	U.S. Patent No. 8,877,776 (Appx10583-10629)
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
¹³ CNMR	carbon-13 nuclear magnetic resonance
Donovan	Dr. Maureen Donovan, MSN's pharmaceutical formulation expert
DSC	differential scanning calorimetry
Exelixis	Plaintiff-Cross-Appellant Exelixis, Inc.
FDA	U.S. Food and Drug Administration
Koleng	Dr. John Koleng, Exelixis' pharmaceutical formulation expert
Lepore	Dr. Salvatore Lepore, MSN's pharmaceutical impurity expert
MacMillan	Dr. David MacMillan, Exelixis' organic impurity expert
Malate salt patents	The '439, '440, and '015 patents

MSN	Defendants-Appellants MSN Laboratories Private Ltd. and MSN Pharmaceuticals, Inc.
Myerson	Dr. Allan Myerson, Exelixis' pharmaceutical formulation expert
NDA	New Drug Application
POSA	person of ordinary skill in the art
ppm	parts per million
PTO	U.S. Patent and Trademark Office
Shah	Dr. Khalid Shah, Sr. Vice President, Exelixis
Steed	Dr. Jonathan Steed, MSN's pharmaceutical salt formation and characterization expert
TGA	thermogravimetric analysis
Trout	Dr. Bernhardt Trout, Exelixis' pharmaceutical salt formation and characterization expert
Wilson	Dr. Jo Ann Wilson, Fmr. Vice President, Exelixis
XRPD	X-Ray Powder Diffraction

STATEMENT OF RELATED CASES

Under Federal Circuit Rule 47.5, Defendants-Appellants (“MSN”)

state as follows:

(a) No previous appeal has been taken in this action.

(b) Plaintiff-Cross-Appellant (“Exelixis”) is also asserting the patents asserted here in *Exelixis, Inc. v. Sun Pharm. Indus. Ltd.*, No. 1:24-cv-01208 (D. Del.). The ’349 patent is also challenged in a petition for *inter partes* review in *Azurity Pharms., Inc. v. Exelixis, Inc.*, IPR2025-00210 (PTAB). Exelixis is also asserting U.S. Patent No. 12,128,039, which is related to the ’349 patent and shares the same specification, in *Exelixis, Inc. v. MSN Labs. Pvt. Ltd. et al.*, No. 1:25-cv-00346-RGA (D. Del.). Counsel is not aware of any other case pending in this or any other court or agency that will directly affect or be directly affected by this Court’s decision in the pending appeal.

INTRODUCTION

This appeal involves four follow-on patents Exelixis obtained on the known drug cabozantinib. Exelixis first claimed the cabozantinib compound and any pharmaceutically acceptable salt thereof in an earlier patent that expires in 2026. Three of the presently asserted patents (the “malate salt patents”) broadly claim *any* crystalline form of the cabozantinib (L)-malate salt, despite narrowly disclosing only *two* closely related crystalline forms that cannot show possession of the entire claimed genus. The fourth asserted patent, the ’349 patent, claims a cabozantinib formulation essentially free of a specific genotoxic impurity—a property inherent in the prior art. All four asserted patents are invalid, and the district court legally and clearly erred in finding otherwise.

The malate salt patents. The written description requirement of 35 U.S.C. § 112(a) “is part of the *quid pro quo* of the patent grant and ensures that the public receives a meaningful disclosure in exchange for being excluded from practicing an invention for a period of time.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1354 (Fed. Cir. 2010) (en banc). An adequate description is one that “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject

matter,” which “depend[s] on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Id.* at 1351. “[T]he purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification.” *Id.* at 1353-54.

The malate salt patents here reflect classic overreach. They claim a broad genus of crystalline forms, or “polymorphs,” of cabozantinib (L)-malate. “Polymorphs are different three-dimensional, solid-state, crystalline structures of the same chemical compound.” *UCB, Inc. v. Watson Labs Inc.*, 927 F.3d 1272, 1276 (Fed. Cir. 2019). Each polymorph is unique and may have wide-ranging effects on stability, storage, manufacturing, and other properties critical to drug development. This Court has previously credited testimony by two experts who testified below that “[d]iscovering new crystalline forms is challenging and unpredictable,” and one “can’t predict in advance the physical properties that a crystalline form will have.” *Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *10 (Fed. Cir. Nov. 15, 2022).

Here, Exelixis invented and disclosed only *two* closely related polymorphs of cabozantinib (L)-malate: “N-1” and “N-2.” Appx21; Appx23. Exelixis initially obtained claims limited to those forms. Appx1896 (453:19-454:18) (Steed). Exelixis previously asserted claims to form N-2 against MSN’s generic cabozantinib product, but Exelixis could not prove infringement because MSN successfully designed around them by inventing its own polymorph—form S, which the patents here do not describe.

See Exelixis, Inc., v. MSN Labs. Pvt. Ltd., No. 19-cv-2017, 2023 WL 315614, at *9-16 (D. Del. Jan. 19, 2023) (“*Exelixis I*”). The PTO granted MSN its own patent on form S, confirming its novelty over Exelixis’ forms. Appx6003, Appx6007 (1:59-63, 2:20-25), Appx6019-6020 (claim 1).

Undeterred, Exelixis went back to the PTO, filing continuation applications that *removed* limitations requiring the specific forms Exelixis invented and broadening the claims to cover *any* “crystalline” cabozantinib (L)-malate salt—including MSN’s form S. These applications issued as the malate salt patents asserted here. As the district court recognized, “‘crystalline’ means what is claimed is all the ‘particular polymorph[s]’ or ‘repeating pattern[s]’ of the cabozantinib (L)-malate [salt],” such that the asserted claims are “genus claims, covering the genus of cabozantinib (L)-

malate salts that are characterized by the common property of being crystalline.” Appx22-23 (alterations original).

An analogous case is *ICU Medical, Inc. v. Alaris Medical Systems, Inc.*, where the plaintiff initially obtained claims to medical valves requiring a specific structure—a “spike”—that the defendant did not infringe. 558 F.3d 1368, 1376, 1380 (Fed. Cir. 2009). The plaintiff filed continuation applications removing the “spike” limitation, resulting in “spikeless (or spike-optional) claims.” *Id.* at 1372, 1377. These “spikeless claims [we]re broader” because they covered devices “that operate with a spike and those that operate without a spike.” *Id.* at 1378. “But the specification describe[d] only medical valves with spikes.” *Id.* Because “a person of skill in the art [‘POSA’] would not understand the inventor ... to have invented a spikeless medical valve,” the spikeless claims were invalid. *Id.*

The district court here declined to follow *ICU*, based on its mistaken assumptions that *ICU* involved a “functional” claim limitation and that “[f]unctional claim limitations require more disclosure” under a “more rigorous” standard. Appx27, Appx24. That was legal error. The invalidated claims in *ICU* did *not* recite any functional limitation, and

regardless, the written description requirement is no less “rigorous” for structural limitations than for functional ones. There is only one written description requirement—the one mandated by Congress in 35 U.S.C. § 112(a) and this Court’s en banc precedent in *Ariad*. For genus claims, the test “requires *a precise definition*, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus *sufficient to distinguish the genus from other materials.*” *Ariad*, 598 F.3d at 1350.¹ “[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.” *Id.*

The district court’s analysis conflicts with the governing test. The court found it sufficient that the specification recites the “chemical name and formula of cabozantinib (L)-malate, as well as that the structure is crystalline.” Appx24. This falls far short of the “precise definition” *Ariad* demands. 598 F.3d at 1350. Although a “chemical name and formula” might distinguish *some* chemical genera, it is undisputed they do not distinguish a genus of polymorphs, which share the same chemical name

¹ All emphases are added unless otherwise noted.

and formula with amorphous—i.e., non-crystalline—forms. Appx126 (1:26-31). This leaves only the label that the compound is “crystalline” (Appx24), which “merely draw[s] a fence around the outer limits of a purported genus.” *Ariad*, 598 F.3d at 1350.

Left uncorrected, the ruling below will have far-reaching consequences, allowing branded drugmakers to preempt all possible polymorphs by disclosing only the general concept of crystallinity. This will stifle innovation and delay generic competition by precluding legitimate design-arounds. Congress enacted the written description requirement precisely to prevent such anticompetitive “attempts to preempt the future before it has arrived.” *Ariad*, 598 F.3d at 1353 (alteration omitted).

The ’349 purity patent. The district court correctly found that MSN does not infringe the sole asserted claim of the ’349 patent because MSN’s accused product does not contain the claimed “glidant.” Appx19. But the court erred in upholding the asserted claim as nonobvious.

The dispositive issue for obviousness is whether the prior art inherently discloses cabozantinib “essentially free” (<200 ppm) of a genotoxic impurity called the “1-1 impurity.” There is no meaningful dispute that all remaining limitations would have been obvious. To prove inherency,

MSN relied on three cabozantinib batches manufactured using the prior art Brown process by the manufacturer Regis. The undisputed evidence showed that Regis followed the Brown process, and all three batches were essentially free of the 1-1 impurity. Exelixis conceded both points.

The district court, however, found *sua sponte* that “it is not clear ... that the Regis process followed the Brown process.” Appx50. The district court disregarded Exelixis’ admissions, pinning its decision on a misinterpretation of a regulatory statement that “[s]ome processing and reagent changes were implemented” for one of Regis’ batches. Appx3115. The district court clearly erred in finding MSN did not prove inherency, when both parties’ experts agreed Regis followed the Brown process and obtained cabozantinib essentially free of the 1-1 impurity.

The district court also erred in discounting expert testimony on the underlying scientific principles explaining why Brown inherently produces cabozantinib essentially free of the 1-1 impurity. Appx50-51. The district court faulted MSN for purportedly failing to prove “the Brown process *does not form* the 1-1 impurity through degradation” at *all* (Appx51), which was not MSN’s burden because the claim requires only cabozantinib *essentially* free (i.e., has <200 ppm) of the 1-1 impurity. The

experts agreed, and the district court found, that a POSA would have expected the Brown process to produce cabozantinib essentially free of the 1-1 impurity—corroborating Regis’ testing.

For these and other reasons below, the findings upholding the malate salt patents and the ’349 patent are both legally and clearly erroneous. This Court should reverse—or at least vacate and remand for the district court to apply the proper legal standard.

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338, and it entered a final judgment of all claims on October 23, 2024. Appx1. MSN timely noticed its appeal on November 22, 2024. Appx2838-2839. Exelixis cross-appealed on November 26, 2024. Appx2840-2841. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF ISSUES

I. Whether the district court legally and/or clearly erred in finding the asserted claims of the malate salt patents adequately described under 35 U.S.C. § 112(a), where the claims broadly cover the genus of *all* crystalline cabozantinib (L)-malate salts, yet the specification discloses structural features and properties of only *two* closely related species.

II. Whether the district court legally and/or clearly erred in finding claim 3 of the '349 patent nonobvious, where the “essentially free” limitation was inherent in the prior art, and the district court found otherwise by (a) adopting a clearly erroneous argument that Exelixis never made; and (b) applying a heightened legal standard to expert testimony that satisfied this Court’s precedent for corroborating inherency.

STATEMENT OF THE CASE

I. The Malate Salt Patents

A. Polymorphs each have their own unique chemical and physical properties, which are unpredictable.

As of the priority date in January 2016, approximately half of FDA-approved drugs included a salt as the active pharmaceutical ingredient (“API”). Appx1890 (428:8-10), Appx1891 (432:25-433:2) (Steed). Salts form when an acid reacts with a base and can exist as either crystalline or amorphous material. Appx20; Appx1890 (431:5-7), Appx1892 (439:9-16) (Steed). Both crystalline and amorphous forms of a salt have the same chemical name and formula. *E.g.*, Appx126 (1:26-31) (identifying

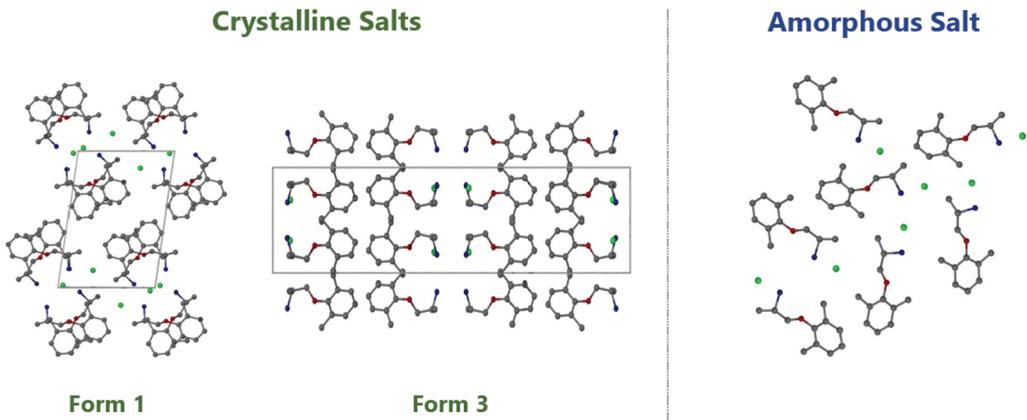
same chemical name and formula for “crystalline and amorphous forms of the malate salts of [cabozantinib]”²).

An amorphous salt does not have any underlying repeating regular arrangement of molecules; instead, the molecules are randomly arranged. Appx1893 (441:6-12) (Steed). By contrast, a crystalline salt has a regular repeating array of molecules that give rise to the crystal structure. Appx20; Appx1892 (439:9-16) (Steed).

Crystalline salts may exist in multiple different crystalline forms, commonly called “polymorphs.” Appx2059 (896:16-18) (Trout). Different polymorphs of the same compound each have different repeating arrangements of molecules. Appx1892-1893 (439:17-440:10) (Steed); Appx2289. Below is a visual example of a compound, xylazine hydrochloride, with the same molecules (i.e., chemical composition and formula) but several different crystalline and amorphous forms:

² “Cabozantinib” is the name for N-(4-{[6,7-bis(methoxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. Appx2281; Appx1889 (427:9-14) (Steed).

Crystalline and Amorphous Salts



DDX(Steed)-11

Appx2289; *see also* Appx1892-1893 (439:7-441:12) (Steed).

Different crystalline polymorphs can arise from preparing a salt using differing circumstances and conditions—e.g., the types and concentrations of solvents, the temperature for the reaction, and the method of preparation. Appx1893-1894 (440:23-441:5) (Steed); Appx2062-2063 (908:24-910:14), Appx2066 (921:16-22) (Trout). A POSA can characterize a compound's crystal structure using x-ray powder diffraction ("XRPD"), which provides a crystalline form's unique "fingerprint." Appx2060 (898:8-10) (Trout); Appx1893 (443:16-19) (Steed). A salt cannot be crystalline without existing in a specific crystalline form, or polymorph. Appx20; Appx1893 (440:15-22) (Steed).

While polymorphs share the same chemical composition (e.g., chemical name and formula), they each have different crystal structures and their own unique physical and chemical properties. Appx1894 (444:19-445:1, 447:9-15), Appx1918 (540:1-9) (Steed); Appx1939 (626:14-23) (Shah) (“Generally speaking, yes. Different polymorphs can have different characteristics” and “different properties”); Appx2065 (917:6-21) (Trout) (“In general, [properties of polymorphs] can differ.”). The prior art teaches that “polymorphism is quite common among organic molecules,” and “[c]rystalline polymorphs have the same chemical composition but different internal crystal structures and, therefore, possess different physico-chemical properties.” Appx3894. The different physical and chemical properties of polymorphs arise from differences in their underlying crystal structures. Appx1893 (443:2-15) (Steed).

A polymorph’s crystal structure is identified by unique inherent physical properties such as different XRPD patterns, melting points, solubilities, densities, hygroscopicity, physical and chemical stability, vapor pressure, processing characteristics, and color. Appx2065 (918:17-919:23) (Trout); Appx1894 (444:19-447:8) (Steed). These unique properties are inextricably connected to “the occurrence of polymorphism

[which] has important formulation, biopharmaceutical and chemical process implications.” Appx6134.

For example, the crystalline form can affect the potency, or bioavailability, of an API, which Exelixis’ expert, Dr. Trout, agreed is “very important in the pharmaceutical world.” Appx2065 (919:24-920:6); *see also* Appx1894 (444:19-445:17, 447:2-8) (Steed). Thus, Dr. Trout agreed it is “important … to identify and isolate different polymorphs of a crystalline salt” (Appx2059 (896:19-22)) because “significant differences in chemical and physical characteristics may arise with changes in crystalline form” (Appx2059-2060 (896:23-897:1)) and “can affect the manufacturability, performance, and quality of a drug product” (Appx2060 (897:2-4)).

Accordingly, FDA guidance—which to Dr. Trout represents “de facto requirements” (Appx2066 (923:7-11))—states that “by the time of a[] [New Drug Application (‘NDA’)] submission, the applicant should have established whether (or not) the drug substance exists in multiple solid-state forms” (e.g., crystalline forms), and the applicant should determine whether the form affects dissolution and bioavailability. Appx3522; *see also* Appx1895 (448:5-11) (Steed). Dr. Trout agreed these

guidelines arise from “the concern [it] might be the case” that “not every polymorph will have a[] [therapeutic] effect.” Appx2066 (923:14-924:1). Thus, as of the priority date, drugmakers essentially always conducted crystalline polymorph screens when developing new drugs. Appx1895 (449:16-19, 450:9-16) (Steed); Appx2062 (907:9-11) (Trout) (“discover[ing] a new [crystalline] form” is “highly unpredictable”).

B. Exelixis initially asserted patents whose claims were limited to the two related polymorphs of crystalline cabozantinib (L)-malate that Exelixis invented and disclosed, which MSN did not infringe.

Exelixis holds the NDA for Cabometyx®, a tablet containing the API cabozantinib (L)-malate,³ first approved in 2016 and indicated to treat kidney, liver, and differentiated thyroid cancer. Appx2-3, Appx1930 (588:6-13) (Shah), Appx10677. Exelixis first invented and evaluated the free base, cabozantinib, in the early 2000s. Appx1929-1930 (587:18-588:5, 589:20-590:1) (Shah). Exelixis filed a patent application claiming cabozantinib “or a pharmaceutically acceptable salt thereof,” which issued on August 25, 2009, as U.S. Patent No. 7,579,473 and

³ Cabozantinib (L)-malate and cabozantinib (s)-malate are the same salt but refer to different naming conventions. Appx3 (n.2).

expires in 2026. Appx11536, Appx11743 (claim 5); Appx1900 (468:23-24) (Steed).

Next, Exelixis partnered with a contract research organization to perform a salt screen and identify salts of cabozantinib for commercial development. Appx1930 (591:12-23) (Shah). By mid-2004, Exelixis selected the crystalline (L)-malate salt. Appx1932 (597:3-9) (Shah). And by 2010, Exelixis had identified and prepared two “closely related” forms of crystalline cabozantinib (L)-malate, N-1 and N-2. Appx1939 (624:24-625:16) (Shah). Indeed, Exelixis reported in its 2015 NDA submission to FDA that “[c]abozantinib ([L])-malate was found to exist in two neat, closely related, crystalline forms (N-1 and N-2) that have similar properties,” and “[n]o other forms were identified.” Appx3053; Appx1939 (627:14-17), Appx1940 (629:15-630:11) (Shah). Exelixis never invented any crystalline form of cabozantinib (L)-malate other than N-1 and N-2. Appx21, Appx2061 (902:15-18) (Trout).

Exelixis filed patent applications with claims to crystalline cabozantinib (L)-malate forms N-2 and N-1, which issued in 2014 and 2017 as U.S. Patent Nos. 8,877,776 and 9,809,549, respectively. Appx10583, Appx10628-10629 (claim 1); Appx10630, Appx10676 (claim

1); Appx1896 (453:19-454:11) (Steed); Appx2296. These patents' claims are narrowly drawn to N-1 and N-2, characterized by specific XRPD peaks and patterns or carbon-13 nuclear magnetic resonance ("¹³CNMR") spectra peaks. Appx10628-10629 (claim 1); Appx10676 (claim 1).

Both the '776 and '549 patents (like the malate salt patents asserted here) share an identical specification.⁴ Appx1896 (453:19-454:2) (Steed). The specification characterizes forms N-1 and N-2 in detail, including with XRPD, thermogravimetric analysis ("TGA"), differential scanning calorimetry ("DSC"), and moisture sorption data. Appx127 (3:50-4:11), Appx99, Appx103-106, Appx110-112; Appx1896 (452:10-453:18) (Steed); Appx2061 (902:19-904:2) (Trout). As Dr. Trout agreed, "[t]here's no description in the specification of any crystalline form [of cabozantinib (L)-malate] other than N-1 and N-2." Appx2061 (904:13-15). And he agreed N-1 and N-2 are the "only working examples" of "crystalline polymorphic forms." Appx2061 (904:19-23); *see also* Appx21.

The specification reports that N-1 and N-2 have unique, beneficial properties over the cabozantinib free base and other cabozantinib salts.

⁴ When referring to the shared specification of the '776, '549, and malate salt patents, we generally cite the '439 patent (Appx93-141) for simplicity and consistency with the trial record.

Appx128-129 (6:56-7:45); Appx1898 (461:14-462:12) (Steed). The specification reports that N-1 and N-2—the only polymorphs Exelixis tested—are “stable up to 185°C,” with no solvent loss in a TGA experiment. Appx129 (7:16-18); Appx1898-1899 (463:25-464:6) (Steed). They have “suitable solubility and chemical/physical stability” (Appx129 (8:23-24)) and are “non-hygroscopic” (Appx129 (8:22)), which is typically preferred to prevent weight changes when developing pharmaceutical formulations (Appx1894 (445:25-446:4) (Steed)). Further, “[t]he uptake of water” by forms N-1 and N-2 is “reversible with a slight hysteresis.” Appx129 (7:18-19). And the specification touts that N-1 and N-2 could be “synthesized with good yield and purity >90% and had sufficient solubility for use in a pharmaceutical composition.” Appx129 (7:21-23).⁵

In August 2019, MSN submitted Abbreviated New Drug Application (“ANDA”) No. 213878 seeking FDA approval for generic cabozantinib (L)-malate tablets. DTX-160.0001; Appx1776 (168:19-169:16) (Koleng).

⁵ The specification refers to “Compound (I)” as having these beneficial properties. See Appx129 (7:10-26). However, while Compound (I) is broadly defined as the (L)-malate salts of cabozantinib (see Appx128 (6:59-61)), which would include all amorphous and crystalline forms, there is no dispute that these reported properties reflect testing on N-1 and N-2—the only polymorphs Exelixis invented and prepared (Appx21; Appx2061 (902:15-18) (Trout)).

MSN certified under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the '776 patent is invalid or not infringed, and Exelixis filed suit. *Exelixis I*, 2023 WL 315614, at *1.

At trial, MSN showed that its accused tablets contain MSN's novel form S of cabozantinib (L)-malate, which MSN formulated as a design-around to Exelixis' forms N-1 and N-2. *Id.* at 11. Indeed, the PTO granted MSN its own patent on form S in March 2022, confirming its novelty over Exelixis' forms. Appx6003, Appx6007 (1:59-63, 2:20-25) (citing N-1 and N-2 as prior art and disclosing novel form S). The court agreed with MSN, issuing an opinion in January 2023 that rejected Exelixis' theory that form S is "unstable" and would convert to form N-2 over time. *Exelixis I*, 2023 WL 315614, at *11.

C. Unable to prove infringement of the two polymorphs it disclosed, Exelixis obtained broad claims to *all* crystalline cabozantinib (L)-malate polymorphs, including those it never invented or disclosed.

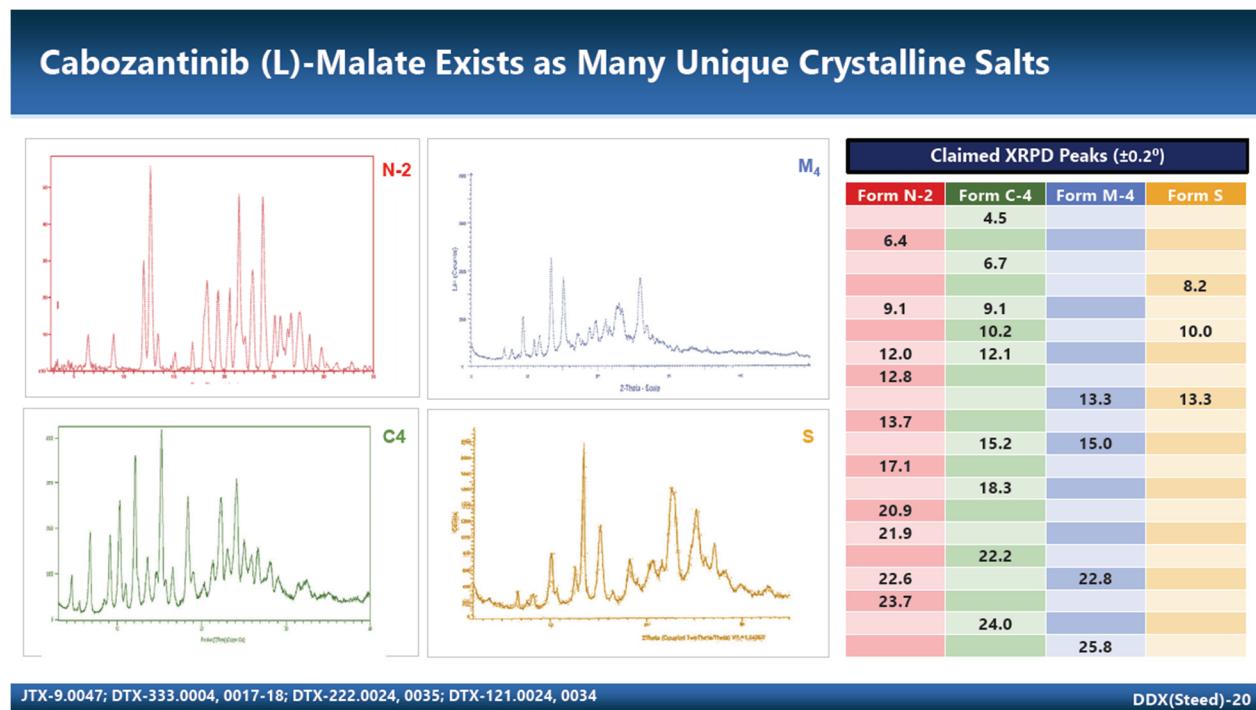
Exelixis did not appeal the *Exelixis I* ruling. Instead, it went back to the PTO during the *Exelixis I* litigation, filing continuation applications in October 2020 and early 2021 that sought broader claims than the '776 and '549 patents' claims, based on the same limited disclosure. Appx94; Appx143; Appx192. The malate salt patents that issued in

August 2021 from these applications claimed and covered *all* crystalline forms of cabozantinib (L)-malate. Appx20; Appx141 (claim 4); Appx190 (claim 3); Appx239 (claim 2); Appx1922 (558:1-6) (Steed).

But Exelixis never invented or disclosed the many dissimilar species of crystalline cabozantinib (L)-malate within this broad genus. Before Exelixis filed the continuation applications that issued as the malate salt patents, four different companies had already filed and published patents and patent applications reporting 11 different crystalline forms of cabozantinib (L)-malate: forms N-1 and N-2 (Exelixis) (Appx10583, Appx10628-10629; Appx10630, Appx10676); form S (MSN) (Appx6003, Appx6019-6020 (claim 1)); forms M1, M2, M3, and M4 (Mylan) (Appx11747 (Abstract)); and C2, C3, C4, and C5 (Cipla) (Appx3275). See Appx21; Appx1896-1897 (455:23-456:12) (Steed).

That patent literature discloses XRPD diffractograms characterizing the unique crystal structures for all 11 reported crystalline forms of cabozantinib (L)-malate. See Appx1896-1897 (455:23-458:4), Appx1923 (560:20-561:19) (Steed); Appx2298; *see also* Appx10615 (3:33-34, 3:47-48), Appx10587 (Fig. 1), Appx10594 (Fig. 8); Appx6008 (3:9-12), Appx6006 (Fig. 6); Apppx11766 (3:28-29, 3:34-35, 3:40-43), Appx11748 (Fig. 1),

Appx11751 (Fig. 4), Appx11754 (Fig. 7), Appx11755 (Fig 8); Appx3277, Appx3299 (Fig. 1), Appx3300 (Fig. 4), Appx3301 (Figs. 5, 6). The examples below highlight these dissimilar crystal structures:



Appx2298; Appx1897 (456:13-458:4) (Steed). Likewise, the patent literature discloses different preparation methods, and Dr. Trout agreed that different preparation methods “lead[] to the difference in the[ir] crystalline structure.” Appx2063 (911:22-912:6); *see also* Appx1897 (458:5-460:3) (Steed); Appx10622-10625 (18:38-23:13); Appx6018-6019 (23:36-25:50); Appx11770-11771 (12:14-13:34); Appx3288-Appx3292.

Disclosed chemical and physical properties that identify other crystalline cabozantinib (L)-malate polymorphs highlight the differences in

their crystal structure from N-1 and N-2. For example, the melting points of forms N-1 and N-2 are 187°C and 186°C, respectively. Appx141 (31:5-7, 31:12-14); Appx1898 (463:3-6) (Steed). By contrast, Mylan's form M-4 has a melting point of 174.87°C, and MSN's form S has a melting point of 113°C. Appx4671; Appx1898 (463:12-20) (Steed). Forms N-1 and N-2 are non-hygroscopic, while MSN's form S is hygroscopic. Appx129 (8:22); Appx1899 (464:24-465:15) (Steed); Appx2067 (925:9-17) (Trout). Forms N-1 and N-2 are non-solvated forms of crystalline cabozantinib (L)-malate that are stable (show no solvent loss) up to 185°C in a TGA experiment. Appx129 (7:16-18); Appx1898-1899 (463:25-464:6) (Steed). Mylan's form M-1 is a solvated crystalline form that shows 4.26% solvent loss in a TGA experiment. Appx4665; Appx1899 (464:15-23) (Steed). And MSN's form S is a hydrated crystalline form (i.e., a solvated form where the solvent is water). Appx1923 (562:8-11) (Steed). Based on this wide variation in properties, MSN's expert, Dr. Steed, testified that forms N-1 and N-2 are not representative of other crystalline cabozantinib (L)-malate salts that exist or that a POSA could reasonably expect to exist. Appx1899 (466:1-14) (Steed); *see also* Appx1898-1899 (463:7-11, 464:8-14, 465:11-15, 465:16-25) (Steed).

Exelixis' expert, Dr. Trout, agreed that a POSA "would not know whether other ... crystalline forms [of cabozantinib (L)-malate] even existed based on the disclosure" in the malate salt patents. Appx2062 (905:3-8). He further agreed "there is nothing in the specification that enables [a POSA] to predict whether there would be other forms." Appx2062 (905:9-12). Dr. Trout called the range and combinations of crystal growth structures "virtually infinite." Appx2066 (922:10-17).

D. The district court upheld Exelixis' broad claims, despite agreeing that they cover an entire genus of polymorphs while disclosing only two species.

In its October 2024 opinion underlying this appeal, the district court agreed with MSN that the malate salt patents claim a genus, finding that "[a]ll crystalline cabozantinib (L)-malate salts fall within [the] scope' of the asserted claims." Appx20; *see also Billups-Rothenberg, Inc. v. Associated Reg'l & Univ. Pathologists, Inc.*, 642 F.3d 1031, 1037 (Fed. Cir. 2011) ("A claim encompassing two or more disclosed embodiments within its scope is a genus claim."). The court also agreed that Exelixis did not invent or possess any crystalline form of cabozantinib (L)-malate other than N-1 and N-2. Appx21, Appx23. And it found that "N-1 and N-2 are the only forms disclosed in the specification." Appx23.

Nevertheless, the district court rejected MSN's written description defense by finding that the specification discloses "structural features common to the members of the genus so that [a POSA] can visualize or recognize the members of the genus." Appx23 (cleaned up). The court relied on the disclosure of the "chemical name and formula of cabozantinib (L)-malate," which applies equally to the amorphous form of the compound that lies outside the claimed genus, and the fact that the claimed compounds are "crystalline"—the same word used in the claims to outline the scope of the genus. Appx24. The district court did not determine the number of species within the genus or whether the disclosed forms N-1 and N-2 are representative of other species, finding it did not need to resolve these issues. Appx21 (n.7), Appx25.

II. The '349 purity patent

Asserted claim 3 of the '349 patent requires a composition comprising cabozantinib (L)-malate and certain well-known excipients, wherein the composition is "essentially free" of (i.e., contains <200 ppm) 6,7-dimethoxy-quinoline-4-ol (the "1-1 impurity"). Appx45.

Formulating cabozantinib with the claimed excipients—filler, lubricant, disintegrant, and glidant—was known in the art and could be

“prepared according to methods available to the skilled artisan.” Appx84 (18:24-25), Appx86 (21:37-45). The specification admits that “known techniques for [] bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions [of claim 3 of the ’349 patent] and are described in [prior-art formulation texts].” Appx85 (20:36-52); Appx1883 (401:7-13) (Donovan).

Claim 3’s alleged novelty is its requirement that the composition be “essentially free” of the 1-1 impurity. Appx48. The “key feature” to formulating a composition essentially free of the 1-1 impurity is starting from cabozantinib API that itself is essentially free of the impurity. Appx55, *see also* Appx47. Thus, the disputed issue at trial was whether “making cabozantinib (L)-malate API essentially free of the 1-1 impurity would have been obvious to a POSA.” Appx48 (cleaned up).

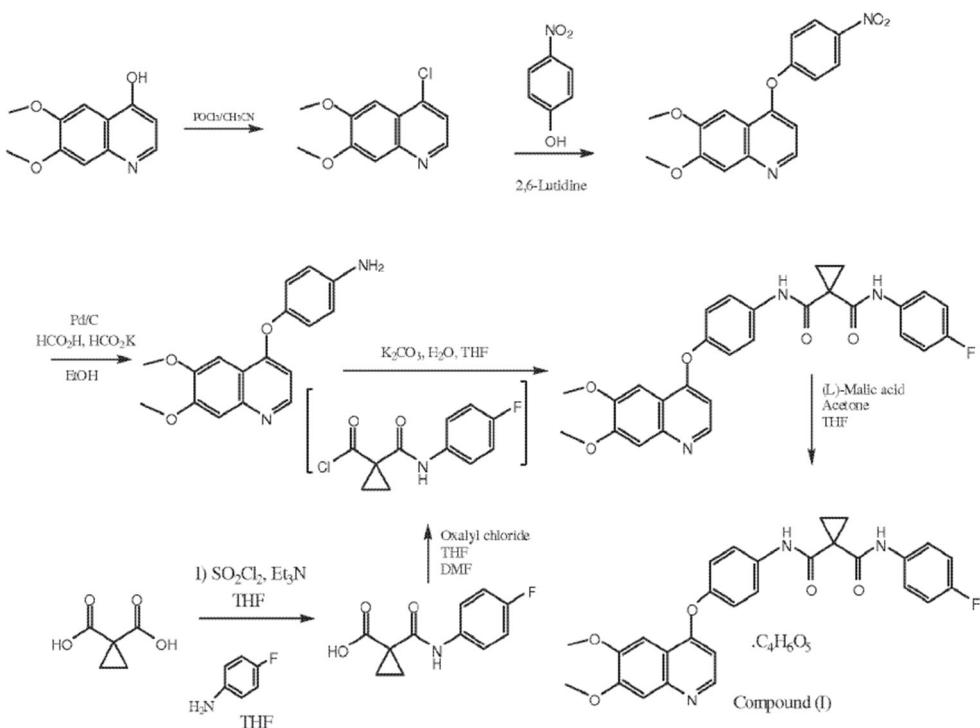
A. Brown disclosed cabozantinib (L)-malate essentially free of the 1-1 impurity.

MSN asserted that the prior art inherently disclosed cabozantinib (L)-malate essentially free of the 1-1 impurity. Exelixis’ 2010 International Patent Application Publication No. WO 2010/083414 to Brown—specifically, example 1 (the “Brown process”)—inherently produced

cabozantinib (L)-malate API with very low levels of the 1-1 impurity, thus meeting the “essentially free” limitation. Appx49.⁶

Brown “describes how to synthesize cabozantinib (L)-malate API” with a “step-by-step” detailed synthetic scheme (below) and narrative description. Appx45; Appx5852-5855 (¶¶ 0098-00114).

SCHEME 1



Appx45; Appx5852; *see also* Appx5852-5855.

As the district court recognized, “[e]ach step of the Brown process purifies the API.” Appx46. Thus, the Brown process yields cabozantinib

⁶ Brown is the international patent application to which the malate salt patents claim priority and contains the same disclosure. Appx567.

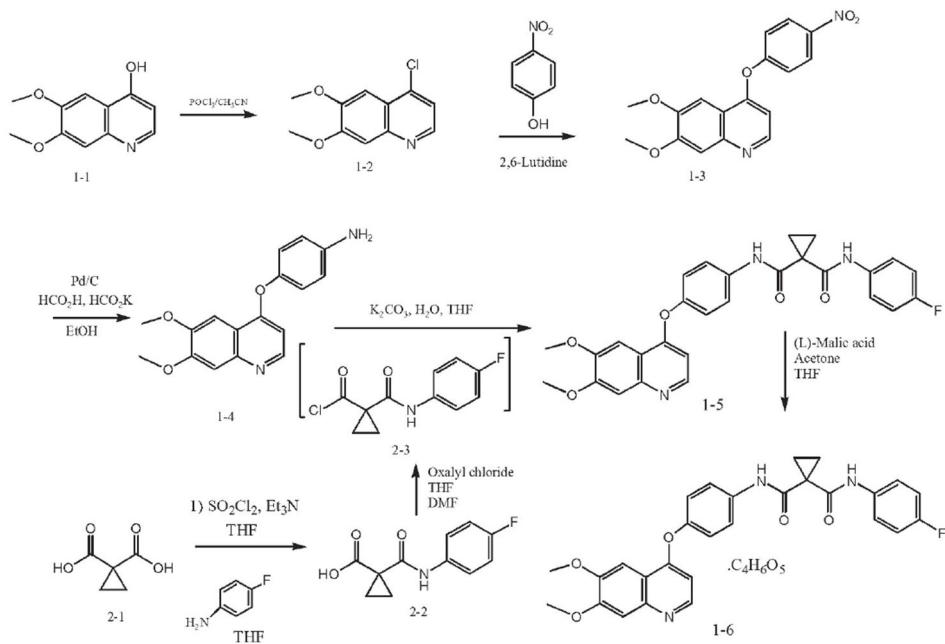
(L)-malate API that is “substantially pure,” which Brown explains can be “about 100%” pure. Appx5851 (¶ 97); Appx1802(269:5-16) (Lepore). Brown further discloses that cabozantinib (L)-malate can be formulated into its “particularly preferred” dosage form as oral capsules or tablets. Appx5849 (¶ 87); Appx1876 (372:2-11), Appx1880 (390:25-391:8) (Donovan). Further, Brown discloses that cabozantinib (L)-malate can be mixed with fillers, disintegrants, lubricants, and talc (a well-known glidant), and formulated by known methods. Appx5848 (¶ 82); Appx1876 (372:20-373:5, 373:10-17), Appx1881 (392:12-20) (Donovan).

B. Following the Brown process, Regis made three batches of cabozantinib (L)-malate “essentially free” of the 1-1 impurity.

Because Brown does not *expressly* disclose the concentration of 1-1 impurity, MSN relied on data for batches that Regis Technologies—an API manufacturer for Exelixis—made and Exelixis tested for the 1-1 impurity to show that the Brown process *inherently* discloses cabozantinib API essentially free of the 1-1 impurity. Appx49. Exelixis contracted with Regis to produce three batches (the “Regis batches”) of cabozantinib (L)-malate between 2005 and 2007. Appx46; Appx1802 (270:21-271:19), Appx1804 (277:7-21) (Lepore) (discussing Appx3219 (Table 1)). Exelixis

included details of those batches in its Investigational New Drug (“IND”) application to FDA, which included a “Description of Manufacturing Process and Process Controls.” Appx3115. The IND disclosed the “synthetic route used for the preparation” of cabozantinib, which had been “used to manufacture multiple lots.” Appx3115. Like Brown, Exelixis included a schematic of the synthetic route:

Figure 7.2-8: Synthetic Route for the Preparation of XL184 Drug Substance



Appx3115; *see also* Appx3115-3118 (narrative description of synthesis).

MSN’s expert, Dr. Lepore, compared the “step-by-step” synthetic scheme and narrative description in Brown side-by-side with the synthetic scheme and narrative description from the Regis process, confirming the two involved “the same chemistry, same schemes,” and were the

“very same process.” Appx1802-1803 (272:19-275:21); compare Appx3115-3118 with Appx5852-5855. Exelixis’ expert, Dr. Myerson, agreed that “[t]he language used by Exelixis in its IND to describe how the clinical material was manufactured [by Regis] is identical to Example 1 Brown.” Appx2032 (786:2-7). Thus, there was no dispute that Exelixis’ scientific description of how Regis manufactured its cabozantinib was identical to the scientific description in Brown.

Additional evidence confirmed the Regis and Brown processes are identical. Exelixis internally referred to the Brown process as “the A-2 process.” Appx45; Appx10845 (Fig. 8); Appx2013 (709:20-23) (Myerson). Exelixis’ regulatory submissions consistently indicated that Regis made its batches following the A-2 process (i.e., the Brown process). Appx10845; Appx10870; Appx2031 (783:7-15) (Myerson). Dr. Myerson testified that Exelixis’ “submissions to the FDA represented that the batches made by the Regis process were made according to ... the Brown process.” Appx2014 (716:18-24) (cleaned up). Exelixis did not dispute that Regis followed the Brown process.

Exelixis also did not dispute that the Regis batches, which Regis made using the Brown process, “all had lower than 100 ppm of the 1-1 impurity and thus met the ‘essentially free’ limitation.” Appx49.

C. The district court found claim 3 of the ’349 patent non-obvious, despite overwhelming evidence that the sole limitation at issue was inherent in the prior art.

The district court analyzed MSN’s use of “inherency in an obviousness argument” by applying a two-prong test requiring both (1) “experimental data showing that the prior art reference inherently discloses the claimed limitation”; and (2) “expert testimony of the underlying scientific principles.” Appx49.

As to the experimental data prong, MSN relied on the Regis batches to show that “if the Brown process is followed, it will inherently result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity.” Appx49. The district court correctly found it “undisputed that the three Regis batches all ... met the ‘essentially free’ limitation.” Appx49. Both parties’ experts agreed that Regis followed the Brown process. Appx2032 (786:2-7), Appx2014 (716:18-24) (Myerson); Appx1802-1803 (272:19-275:21) (Lepore). Despite this consensus, the court found “it was not clear that the Regis process followed the Brown process.” Appx50 (cleaned up).

The district court reached that conclusion on its own; Exelixis never denied that Regis followed the Brown process. Rather, Exelixis *conceded* it “told the FDA” that “[t]he Regis [] batches were made using the process disclosed in Brown.” Appx2763 (¶ 72); *accord* Appx2014 (716:18-24) (Myerson).

The district court cited a passing statement in Exelixis’ IND that “[s]ome processing and reagent changes were implemented” for one of Regis’ batches. Appx3115. The IND does not indicate what the purported “changes” entailed. Rather, it sets forth “the current route and scale used in the production of the drug substance [] at Regis” in detail. *Id.* Nor did Exelixis produce batch records showing any purported “changes” Appx1874 (364:3-364:13) (Lepore); Appx2032 (787:8-22) (Myerson). There was no evidence that the purported changes were anything other than “extremely minor things.” Appx1819 (338:2), Appx1818 (335:19-336:2), Appx1874 (364:3-365:13) (Lepore).⁷

⁷ Instead of disputing that Regis followed the Brown process, Exelixis argued that another manufacturer, Girindus, purportedly followed the Brown process and showed higher levels of 1-1 impurity. The district court, however, “d[id] not consider evidence of the Girindus batch.” Appx49 (n.13). Girindus did not follow the Brown process, committing at least six “deviations” and an “error.” Appx3157-3168; Appx2248; Appx1808 (295:2-5) (Lepore); Appx2033 (791:5-23) (Myerson).

As to the underlying science prong, expert testimony confirmed “each step of the Brown process purifies the API.” Appx46; Appx1950 (668:16-669:14) (MacMillan); Appx2013 (708:23-709:19) (Myerson). As Exelixis’ Nobel Prize-winning chemistry expert, Dr. MacMillan, explained, “a POSA would not expect any 1-1 impurity to be left at the end of Brown, because each of the five steps of Brown has a purification component and the reagents added through the process could purge the impurity.” Appx50-51 (n.14); Appx1950 (668:16-669:14), Appx1949 (677:11-25) (MacMillan); Appx2033 (791:5-23) (Myerson). The district court thus found that any remaining impurity after the Brown process would be “at most, de minimis,” thus meeting the “essentially free” limitation. Appx45-46.

The district court nonetheless held it was “MSN’s burden [] to show that the Brown process *does not form* the 1-1 impurity through degradation.” Appx50. The district court faulted MSN for relying on “testimony of various experts who explain that a POSA would not have expected the 1-1 impurity to form” because “what a POSA would have expected is not sufficient to show inherency.” Appx50-51.

Finally, the district court considered Exelixis' alleged secondary considerations of nonobviousness. Appx57. The court rejected Exelixis' assertions of long-felt unmet need and unexpected results. *Id.* Although the court found commercial success, it found that this "is not a strong indicator of non-obviousness" because Exelixis owned a blocking patent that prevented commercial development of cabozantinib. *Id.*

SUMMARY OF ARGUMENT

I.A. The district court committed three legal errors in finding that the malate salt patents describe sufficient "structural features" to support broad genus claims to *all* crystalline cabozantinib (L)-malate salts—a finding that is at least clearly erroneous.

First, the court legally erred by crediting cursory disclosures that "merely draw[] a fence around the outer limits of a purported genus." *Arriad*, 598 F.3d at 1350. The court relied on the "chemical name and formula of cabozantinib (L)-malate" (Appx24), which are *not* "sufficient to distinguish the genus from other materials," as precedent requires. *Arriad*, 598 F.3d at 1350. *Amorphous* salts of cabozantinib (L)-malate share the *same* chemical name and formula. Appx126 (1:26-31). The district court otherwise relied on a generic disclosure that the compounds are

“crystalline” (Appx24), which merely restates the genus itself and is “not an adequate substitute for … showing that one has invented a genus and not just a species.” *Ariad*, 598 F.3d at 1350.

Second, the district court legally erred in assuming that functional limitations demand “more rigorous requirements” and “more disclosure” than structural limitations. Appx24, Appx27. Yet Section 112(a) mandates the same written description requirement for *all* inventions. The district court misinterpreted this Court’s caselaw and ignored undisputed evidence that polymorphs are structurally unpredictable.

Third, the district court legally erred in discounting differences in physical properties within the claimed genus. Unrebutted evidence showed that different polymorphs are identified by their vastly different intrinsic properties that reflect their different crystal structures, yet the specification undisputedly describes the properties of *only* two species. Such differences in “physical properties, or other properties,” are highly relevant to determine whether the specification provides the “precise definition” that precedent requires. *Ariad*, 598 F.3d at 1350.

I.B. Because the district court declined to resolve the size of the genus or whether the two disclosed species are “representative” (Appx25),

this Court should at least vacate the judgment. On the undisputed record, however, this Court should reverse outright and hold that N-1 and N-2 are *not* representative species. For example, MSN’s form S has significantly different physical properties that were entirely unknown and unpredictable to Exelixis’ inventors, which confirms they lacked possession of the broad genus that Exelixis claimed.

II.A. In holding claim 3 of the ’349 patent nonobvious, the district court clearly erred in finding it “not clear” that Regis followed the Brown process. Exelixis conceded that Regis *did* follow the Brown process, and expert testimony from both sides established that the process necessarily produces cabozantinib essentially free of the 1-1 impurity.

II.B. In discounting expert testimony on inherency, the district court legally erred in finding it was MSN’s “burden ... to show that the Brown process does not form the 1-1 impurity through degradation” at all. Appx51. MSN’s burden was only to show that Brown inherently disposes what the asserted claim requires—i.e., cabozantinib “*essentially free*” of the 1-1 impurity. *See Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (inherency requires “*the limitation at issue* necessarily must be present, or the natural result of ... the prior

art”); *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014) (faulting inherency analysis that “ignore[d] the claim limitations at issue”).

The district court also legally erred by finding MSN’s corroborative scientific evidence insufficient because it purportedly only showed what a POSA “would have expected.” Appx50. The undisputed expert testimony explained why—as a scientific matter—following the Brown process (as Regis did) necessarily results in cabozantinib essentially free of the 1-1 impurity, and a POSA’s scientific expectation can be sufficient to find inherency. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (where there was “no dispute that the [claimed] blood serum concentrations [we]re *expected* in light of the dosages,” the limitation was “an inherent property”).

At a minimum, the district court clearly erred in finding the 1-1 impurity “could have formed” and “did form” as a degradation product during the Brown process. Appx51. Both parties’ experts *agreed* that following the Brown process results in API essentially free of the 1-1 impurity. Thus, even if 1-1 impurity did form as a degradation product, it was undisputed the impurity was subsequently purged during later steps

of the Brown process, such that “there is, at most, de minimis impurity left at the end of the Brown process.” Appx46.

STANDARD OF REVIEW

Whether a patent complies with “the written description requirement is a question of fact, which this court reviews for clear error” after a bench trial. *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1345 (Fed. Cir. 2010). A tribunal “legally err[s] in its analysis of whether [a] patent complies with the written description requirement,” however, when it fails to apply “the proper legal standard.” *In re Glob. IP Holdings LLC*, 927 F.3d 1373, 1377-78 (Fed. Cir. 2019).

“The ultimate conclusion of whether a claimed invention would have been obvious is a question of law reviewed de novo based on underlying findings of fact reviewed for clear error.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007).

ARGUMENT

I. The asserted claims of the malate salt patents are invalid for lacking written description.

In obtaining the malate salt patents, Exelixis failed to meet its end of the patent bargain. Unhappy with earlier claims that were limited to the polymorphs disclosed in the specification, Exelixis broadened its

claims to cover *all* crystalline cabozantinib (L)-malate salts—including MSN’s novel form S that Exelixis did not possess. The written description requirement of 35 U.S.C. § 112(a) “plays a vital role in curtailing” such claims, which overreach beyond a patentee’s contribution by ensnaring structures “that have not been invented, and thus cannot be described.” *Ariad*, 598 F.3d at 1352.

“Written description of an invention claimed as a genus of chemical compounds … requires description *not only of the outer limits of the genus but also of either [1] a representative number of members of the genus or [2] structural features common to the members of the genus, in either case with enough precision that a relevant artisan can visualize or recognize the members of the genus.*” *Regents of the Univ. of Minn. v. Gilead Scis., Inc.*, 61 F.4th 1350, 1356 (Fed. Cir. 2023) (citing *Ariad*, 598 F.3d at 1350-52). Under either prong, “[a] broad outline of a genus’s perimeter is insufficient.” *Id.*

Here, the district court upheld the asserted claims based solely on the “structural features” prong (Appx23), but its analysis is both legally flawed and clearly erroneous. *Infra*, Part A. Because the “structural features” prong does not support the claims, and the district court did not

address the “representative species” prong, this Court should at least vacate the judgment. On this record, however, the Court should reverse outright, because the malate salt patents clearly do *not* disclose a representative number of species. *Infra*, Part B.

A. The specification fails to disclose structural features to distinguish the genus of crystalline cabozantinib (L)-malate and to visualize its members.

It is undisputed that the structure and properties of each crystalline cabozantinib (L)-malate salt are unique, yet the specification discloses the structure and properties of only *two* forms. *See Appx23*. Likewise, the only “methods of preparation for crystalline cabozantinib (L)-malate” are “methods of preparing the N-1 and N-2 form,” and no other forms. *Appx24*. The specification does *not* disclose the properties that identify the crystal structure of MSN’s form S, for example, or any method of producing it.

While the district court declined to decide how many more species the genus contains (*Appx25*), at least seven other cabozantinib (L)-malate polymorphs are presently known (*Appx21, supra 19*); there could be up to 14 “pure” crystal forms (*Appx21*); and the claims broadly cover any possible “combinations of crystal growth structures [that] are virtually

infinite” (Appx2066 (922:12-17) (Trout)). Each polymorph of cabozantinib (L)-malate has its own unique physical properties, including melting points, hygroscopicity, solvation states, and solubilities—yet the specification discloses such properties *only* for N-1 and N-2. *Supra* 19-21; Appx23.

On this record, the specification clearly fails to disclose sufficient “structural features … with enough precision that a relevant artisan can visualize or recognize the members of the genus.” *Regents*, 61 F.4th at 1356. In finding otherwise, the district court legally erred by (1) relying on “a broad outline of [the] genus’s perimeter” (*id.*); (2) applying a less “rigorous” standard for written description (Appx24); and (3) discounting differences in “physical properties,” which characterize the crystalline structural form of polymorphs and bear upon the genus’s “precise definition” (*Ariad*, 598 F.3d at 1350).

1. The district court legally erred by crediting “a broad outline of [the] genus’s perimeter.”

In concluding that the claims are adequately described, the district court relied on the specification’s disclosure of “[1] the chemical name and formula of cabozantinib (L)-malate, as well as [2] that the structure is crystalline,” and “[3] general methods of forming a crystalline salt” along

with “methods of preparing the N-1 and N-2 form.” Appx24; *see also* Appx25. Under this Court’s precedent, these factual findings cannot support the full scope of the claims.

First, “the chemical name and formula of cabozantinib (L)-malate” (*id.*) are legally insufficient under this Court’s precedent that “an adequate written description requires a precise definition ... *sufficient to distinguish the genus from other materials.*” *Ariad*, 598 F.3d at 1350. It is undisputed “the chemical name and formula of cabozantinib (L)-malate” are the *same* for both crystalline *and* amorphous forms. Appx127 (3:30-32) (specification admitting “[t]he novel salt form of the invention exists in crystalline and amorphous forms”); Appx126 (1:26-31) (identifying same chemical name and formula for “crystalline and amorphous forms of the malate salts of [cabozantinib].”) Thus, “the chemical name and formula of cabozantinib (L)-malate” cannot describe the genus.

It is no answer that a “formula” and “chemical name” might suffice to define *some* chemical genera. *See Ariad*, 598 F.3d at 1350. Nothing in *Ariad* or its progeny suggests this information is sufficient in every case. Here, given the undisputed nature of crystalline polymorphs, which share the same formula and chemical name with an amorphous form of

the same compound, the specification would need to disclose additional “physical properties, or other properties,” to provide “a precise definition” of the claimed genus, as this Court’s precedent requires. *See id.*

Second, that “the structure is crystalline” (Appx24) is legally insufficient under this Court’s precedent that “[a] broad outline of a genus’s perimeter is insufficient.” *Regents*, 61 F.4th at 1356. “[A]n adequate written description of a claimed genus requires more than a generic statement of an invention’s boundaries,” and “merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.” *Ariad*, at 1349-50.

Disclosing “the structure is crystalline” (Appx24) merely restates the genus of “crystalline” cabozantinib (L)-malate, without *any* common structural features or defining properties for the claimed “crystalline” forms. As Dr. Trout agreed, there is a “difference in the crystalline structure” between Exelixis’ form N-2 and MSN’s form S. Appx2063 (912:4-6). And the patent literature discloses different crystalline structures for *each* form of crystalline cabozantinib (L)-malate. *Supra* 19-20.

“To satisfy the written description requirement in the case of a chemical or biotechnological genus, more than a statement of the genus is normally required.” *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1126 (Fed. Cir. 2008). The undisputed unpredictability of polymorphs only reinforces the need for disclosure. *See Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1339 (Fed. Cir. 2021) (“general assertions of structural commonalities, in the context of the technology in this case, are insufficient”).

Third, the disclosed “general methods of forming a crystalline salt” and specific “methods of preparing the N-1 and N-2 form” (Appx24) are equally insufficient as a matter of law. “[T]o satisfy the statutory requirement of a description of the invention, it is not enough for the specification to show how to make and use the invention, i.e., to enable it.” *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1377 (Fed. Cir. 2017). The district court did not explain how “general methods” for forming a crystalline salt or for preparing two species (Appx24) define “*structural* features,” let alone features “common to the members of the genus ... with enough precision” to “visualize or recognize” each member (*Regents*, 61 F.4th at 1356).

Dr. Trout conceded the “difference” in “manufacturing process” “leads to the differences in the crystalline structure” of different cabozantinib (L)-malate polymorphs. Appx2063 (911:22-912:6). By focusing on preparation methods, the court legally erred by asking whether a POSA “would have been *enabled*” to make certain species, instead of “whether the [specification] *discloses* [other] variants to him, specifically, as something [Exelixis] actually invented.” *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350 (Fed. Cir. 2013) (cleaned up).

To the extent preparation methods are relevant, it is undisputed—and the district court found—that the only disclosed methods for preparing crystalline cabozantinib (L)-malate produce *only* N-1 or N-2—not any other species within the claimed genus. Appx21. The specification does *not* disclose a process for preparing form S, or any other crystalline form. Appx21. This limited disclosure does not “sufficiently demonstrate[] that the inventors possessed the *full scope* of the claimed invention,” as Section 112(a) requires. *Juno*, 10 F.4th at 1336.

In short, the district court legally erred by relying on (1) features that are not “sufficient to distinguish the genus from other materials” (*Ariad*, 598 F.3d at 1350); (2) “[a] broad outline of [the claimed] genus’s

perimeter” (*Regents*, 61 F.4th at 1356); and (3) process steps that do not disclose any structural features and are not commensurate with the full scope of the claims. At a minimum, the district court clearly erred in finding these superficial disclosures sufficient.

2. The district court legally erred in applying a less “rigorous” test for written description merely because the disputed claim limitation is structural.

The district court ultimately failed to apply the proper legal standard, crediting clearly deficient disclosures, because it erroneously assumed there are “*more rigorous requirements* for written description in support of functional claim language,” which the court believed “require *more disclosure* to meet the written description requirement.” Appx24, Appx27. Put differently, the district court applied a *less* “rigorous” test requiring *less* “disclosure” for the *structural* genus claimed here.

In bifurcating the written description requirement into different disclosure thresholds depending on whether limitations are “functional” or “structural,” the district court legally erred. There is only *one* written description requirement, which does not distinguish between “functional” and “structural” limitations. *See* 35 U.S.C. § 112(a) (“The specification shall contain a written description of the invention....”). Likewise, en

banc precedent requires a written description that conveys “possession of the claimed subject matter,” regardless of whether inventions are claimed structurally or functionally. *Ariad*, 598 F.3d at 1351.

To be sure, overbroad claiming may be “especially acute with genus claims that use functional language to define the boundaries of a claimed genus” (*id.* at 1349), especially “where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus” (Appx27 n.9) (quoting *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014)). But it does not follow that structural limitations require less “rigorous” analysis or “disclosure.” The legal standard is the same. While structural limitations may be more predictable than functional limitations in *some* fields, that is decidedly not true for polymorphs, whose unique structures and resulting physical properties are notoriously diverse and unpredictable. *Supra* 9-14; *Pharmacyclics*, 2022 WL 16943006, at *10 (one “can’t predict in advance the physical properties that a crystalline form will have”).

Nevertheless, the district court derived a purported legal principle that structural limitations require less disclosure from this Court’s

decision in *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725 (Fed. Cir. 2014) (“GSK”). See Appx23-24. The district court then used this purported principle to distinguish *ICU Medical*, 558 F.3d 1368, which the district court believed was limited to “functional” limitations. Appx27. In analyzing both cases, the district court legally erred.

a. GSK did not diminish the written description requirement for structural limitations that reflect the point of novelty.

The district court relied heavily on statements near the end of this Court’s *GSK* opinion that the disputed claim term—“solvate”—was “not functional.” Appx24 (citing *GSK*, 744 F.3d at 731 (“Critically, moreover, the claim term at issue, ‘solvate,’ is not functional: to be a ‘solvate,’ a compound need not produce a desired result or otherwise perform a certain function.”)). The specification in *GSK*, therefore, did not need to describe any unclaimed functions or teach skilled artisans how to distinguish between solvates that perform specific functions. Yet the lack of functional limitations did *not* exempt the claims’ *structural* limitations from written description support. To the contrary, this Court analyzed both the specification and state of the art to ensure that the claimed structural genus was adequately described. See *id.* at 730-31.

That analysis, which this Court summarized as important “context” when noting the lack of functional limitations (*id.* at 731), illustrates why *GSK* is inapposite. The disputed “solvates” were *not* a point of novelty for the patent at issue. Instead, it was the novel chemical compound, dutasteride, that provided “the key structural feature” distinguishing the claims “from the prior art.” *Id.* at 725. As to *that* “key structural feature,” there was “no[] dispute that dutasteride is adequately described: it [wa]s precisely identified by structure.” *Id.* at 725, 728.

In contrast, (i) “solvate formation ha[d] been known in the art for over 100 years,” (ii) other steroids like dutasteride were “known to be prone to solvate formation,” and (iii) “the universe of solvents thought to be pharmaceutically acceptable was well-known and relatively small.” *Id.* (quotations omitted). Solvates, therefore, were not a point of novelty, and the high-level discussion of solvates in the specification both reflected their conventionality and “match[ed] the claim scope.” *Id.* at 731. It also was “undisputed that the written description enable[d] a [POSA] to make and use the full claimed range of ‘solvates’ of dutasteride.” *Id.*

None of that is true here. The chemical compound cabozantinib is *not* the point of novelty; the patent disclosing cabozantinib is prior art

that expires in 2026. Appx11743 (claim 5); Appx1900 (468:23-24) (Steed); Appx126-127 (2:64-3:19). Rather, the alleged novelty is the structure and identifying inherent physico-chemical properties of specific salt forms—N-1 and N-2, which are the only crystalline species the specification discloses by identifying the novel and beneficial properties that allegedly distinguish the claimed invention from the prior art. *Supra* 16-17. Given the detailed focus on N-1 and N-2, this is not a case where the specification “matches the claim scope.” *Id.* at 731.

Nor is this a case where the art is predictable, the claimed structures are conventional, or the described methods enable skilled artisans to practice the full scope of the claims. Unlike the “well-known and relatively small” universe of solvents in *GSK* (*id.* at 725), Exelixis’ expert admitted “[t]he range and combinations of crystal growth structures are virtually infinite” (Appx2066 (922:12-17) (Trout)), and it is undisputed that N-1 and N-2 are the *only* crystalline forms of cabozantinib (L)-malate known as of the priority date (Appx1939 (627:14-17) (Shah)).

Moreover, while the claims here recite no explicit functional limitations, the identity and alleged utility of the claimed crystalline forms lay in their “properties relating to processing, manufacturing, storage

stability, and/or usefulness as a drug,” which distinguishes them from the prior art. Appx127 (3:22-23); *see also supra* 16-17. It is undisputed that not all crystalline forms will share these properties that the specification touts for N-1 and N-2. Appx2065 (917:6-21) (Trout) (“In general, [properties of polymorphs] can differ”); *supra* 12-14, 20-22. By contrast, in *GSK*, “the specification itself suggest[ed] that any one of the solvate forms will suffice equally.” *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, No. 11-cv-046, 2013 WL 4082232, at *5 (D. Del. Aug. 9, 2013), *aff’d*, 744 F.3d 725.

GSK, therefore, is inapposite, and it does not alter the requirement for written description support of structural limitations—especially when, as here, the structure of “crystalline” forms is critical to the point of novelty and to the invention’s alleged utility.

b. The invalidated claims in *ICU Medical*, which did not contain any functional limitations, are closely analogous to Exelixis’ litigation-inspired claims.

Apart from misinterpreting *GSK*, the district court legally erred in distinguishing *ICU Medical*, which is directly on point. There, the patentee initially obtained claims to medical valves with a “spike,” which the specification described but the defendant did not infringe. *ICU Med.*,

558 F.3d at 1374-76. The patentee later obtained new claims *omitting* the “spike” limitation, which this Court called “spikeless (or spike-optimal) claims.” *Id.* at 1372-73. The Court “refer[red] to these claims as spikeless not because they exclude[d] ... a spike but rather because these claims d[id] not include a spike limitation—i.e., they d[id] not require a spike” in the claimed structure. *Id.* at 1377. These “spikeless claims [we]re broader than [the] spike claims because they d[id] not include a spike limitation” and thus “cover[ed] those valves that operate with a spike and those that operate without a spike.” *Id.* at 1378.

This Court held that the broad, “spikeless” claims lacked written description—not because they lacked support for any functional limitations, but because “the specification describe[d] only medical valves with spikes,” and a POSA “would not understand the inventor of the [] patents to have invented a spikeless medical valve.” *Id.*

The facts here closely track *ICU Medical*. As discussed, Exelixis originally asserted patents whose claims required form N-2. Exelixis failed to prove infringement of those claims. *See Exelixis I*, 2023 WL 315614, at *9-16. Exelixis thus prosecuted new applications that *removed* limitations requiring form N-2 and *broadened* the claims to cover

all “crystalline” cabozantinib (L)-malate salts, significantly expanding the claim scope in a transparent attempt to ensnare form S that MSN independently developed. *Supra* 18-19.

Despite these close parallels, the district court distinguished *ICU Medical* solely “because in that case the spike limitation was functional,” given the construction of “spike” as “having a pointed tip for piercing the seal.” Appx27. Whether “spike” has a particular function, however, is irrelevant because the claims invalidated in *ICU Medical* “d[id] not recite any spike limitation.” 558 F.3d at 1377. The invalidity decision in *ICU Medical* did not turn on any functional limitation or ambiguity about which structures satisfy the functional requirements of a “spike.” It was the *absence* of any “spike” limitation that created a written description problem—and not because of any functional uncertainty but because the specification failed to describe the *structure* of any valve lacking a spike. Similarly, the specification here fails to describe the *structure* of any crystalline form lacking the identifying properties unique to N-1 and N-2.

Notably, Exelixis did *not* argue below that *ICU Medical* involved functional claiming. Exelixis conceded that “[s]piked and spikeless medical valves *have different structural features*, based on whether or not

they include the spike element.” Appx2688. Yet the district court made up its own distinction *sua sponte* based on a misreading of *ICU Medical* that neither party advocated. That was legal error.

c. Other cases confirm that a genus claimed with a structural limitation requires written description for the entire genus.

ICU Medical is not an outlier; this Court has invalidated genus claims defined by structural limitations in other cases that are equally analogous and confirm that the district court erred.

In *Tronzo v. Biomet, Inc.*, this Court reversed a judgment finding written description support for claims to a “cup” implant that were “generic as to the shape of the cup.” 156 F.3d 1154, 1158 (Fed. Cir. 1998). The specification “disclose[d] only two species of cups,” both conically shaped, despite claiming a broader genus of cups regardless of shape. *Id.* at 1159. Without deciding how many species the genus contained, this Court held the specification did not support genus claims covering non-conical cups, including the accused hemispherical cup. *Id.* The specification “disclose[d] only conical shaped cups and nothing broader,” which “d[id] not support the later-claimed, generic subject matter.” *Id.*

This Court’s decision in *Tronzo* turned on the structural breadth of the “cup” genus and not on any functional limitation. Indeed, when discussing infringement for narrower claims that *were* limited to conical cups, the Court noted that “the evidence tended to demonstrate that the shape of the cup was irrelevant to achieving the desired result and that after successful implantation any shape would function essentially the same way,” even though “various shapes could produce forces that might be different.” *Id.* at 1160 (quotation omitted).

Similarly, in *Eli Lilly*, this Court invalidated a claim with only structural limitations for lacking written description because of the claim’s breadth. 619 F.3d at 1344-45. The claim recited the compound raloxifene “in particulate form” defined by the property of a maximum particle size, without any functional limitations. *Id.* at 1336. To show infringement, the patentee persuaded the district court “that the limitation ‘in particulate form’ ... should be construed broadly to include raloxifene particles both before and after formulation.” *Id.* at 1344.

That broad claim scope, however, resulted in invalidity because the “specification only disclose[d] measurements of bulk raloxifene” and did not show “the inventor possessed the invention of formulated raloxifene

falling within the claimed size range.” *Id.* at 1345. This conclusion was based entirely on structural limitations—“particulate form” defined by particle size properties—without functional requirements.

Tronzo and *Eli Lilly* confirm that the written description requirement for genus claims applies equally to structural limitations. By assuming otherwise, the district court legally erred.

3. The district court legally erred in discounting differences in physical properties among members of the claimed genus.

The district court acknowledged MSN’s evidence that different crystalline forms have “different densities, melting points, solubilities, hygroscopicity, vapor pressure, and stability”; that “the properties of one crystalline form cannot be used to predict the properties of a different form”; and that “the properties of the known crystalline forms of cabozantinib (L)-malate differ.” Appx25-26. The court did not question this evidence. Instead, the court simply discounted the evidence, believing it lacked a “framework” to evaluate different physical properties. Appx26.⁸

⁸ The court also stated that it could not conclude these physical properties are “so different” that N-1 and N-2 are “unrepresentative.” Appx26. It is unclear what the court meant by this, given its statement in the immediately preceding paragraph that it “need not determine” whether N-1

The relevant framework, however, was the same inquiry discussed above—i.e., whether the specification describes “structural features *common to the members of the genus* so that [a POSA] can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350. Whether the specification discloses “physical properties” shared by members of the genus is highly relevant to that inquiry. *See id.* (“[A]n adequate written description requires a precise definition, such as by structure, formula, chemical name, *physical properties, or other properties*, of species falling within the genus sufficient to distinguish the genus from other materials.”).

That is especially true for polymorphs, which are identified and characterized by physical properties, as opposed to a chemical name or formula that polymorphs necessarily share with amorphous forms. *Supra* 9-10. Here, however, the specification does not disclose physical properties common to the genus’ members. It only discloses properties unique to N-1 and N-2. *E.g.* Appx129 (7:16-18, 8:22-24), Appx141 (31:5-7, 31:12-14); *supra* 16-17. Nor does the specification disclose ranges that

and N-2 are “representative” species, or even how many species the genus contains. Appx25. To the extent this statement relates to the “representative species” prong, we address it in the following section.

could cover the properties of other species. On the contrary, the specification concedes its disclosure is limited to forms “possessing *similar or identical physical* and chemical *characteristics* ... in accordance with the characterization information presented herein.” Appx129 (7:3-9). This confirms a lack of written description. *See Tronzo*, 156 F.3d at 1159 (inadequate description where specification “does not attempt to identify other, equally functional shapes or talk in terms of a range of shapes”).

The district court thus legally erred in discounting the specification’s failure to disclose structure-defining physical properties common to the members of the claimed genus. The court’s conclusion that the specification discloses sufficient structural features to visualize or recognize those members was at least clearly erroneous.

B. The specification narrowly discloses only two related polymorphs—but discloses neither MSN’s form S nor a representative number of species to describe claims covering the entire genus.

The district court relied solely on the “structural features” prong of the written description test and declined to address the “representative species” prong. Appx25 (“I need not determine the size of the genus and whether Exelixis disclosed a representative number of species.”); Appx21

n.7; Appx23. At a minimum, therefore, this Court should vacate the judgment because the district court did not reach this alternate inquiry.

Nevertheless, this Court should go further and reverse the judgment—holding instead that the claims are invalid for lacking written description—because a remand on this record would be futile. *See Trustees in Bankr. of N. Am. Rubber Thread Co. v. United States*, 593 F.3d 1346, 1357 (Fed. Cir. 2010) (“Because remand would be futile, we do not remand for further proceedings.”).

It is undisputed that Exelixis “did not invent any crystalline form of cabozantinib (L)-malate other than Forms N-1 and N-2”—“the only forms disclosed in the specification.” Appx21; Appx23. It is equally undisputed that MSN’s form S is an additional species that Exelixis did not possess. Appx21. And it is undisputed that the physical properties of form S differ significantly from the closely related properties of N-1 and N-2—e.g., their XRPD patterns are completely dissimilar, form S’s melting point is significantly lower (113°C vs. 186-187°C for N-1 and N-2), and form S is hygroscopic, unlike N-1 and N-2. Appx2298; Appx1897 (456:13-458:4) (Steed); Appx1898 (463:3-6), Appx1899 (464:24-465:15) (Steed); Appx2067 (925:9-17) (Trout); *supra* 19-22.

Moreover, Exelixis tried and failed to show that form S infringes claims limited to form N-2 using multiple tests—findings Exelixis did not appeal. *Exelixis I*, 2023 WL 315614, at *10-16. The PTO also granted MSN its own patent to form S, notwithstanding Exelixis’ prior disclosure of N-1 and N-2, which confirms that form S is patentably distinct. *See* Appx6007 (1:59-63, 2:20-25).

On this record, any finding that N-1 and N-2 are representative of the claimed genus, including MSN’s form S, would be clearly erroneous. That is true even without deciding whether additional species exist (they do)—an issue the district court declined to reach despite acknowledging that “[t]here may be up to seven additional identified species.” Appx21. It is also true regardless of the court’s finding that “[t]he maximum potential size of any pure polymorph genus is fourteen forms” (*id.*), which does not include solvates that also fall within the claimed genus. Appx1919 (545:19-547:1), Appx1923 (561:20-562:7) (Steed). As Dr. Trout admitted, the possible “combinations of crystal growth structures are virtually infinite.” Appx2066 (922:12-17).

No matter the precise size and contours of the genus, the *only* species Exelixis disclosed are the two closely related forms N-1 and N-2,

which “abide in a corner of the genus” and do “not describe[] the genus sufficiently to show that the inventor invented, or had possession of, the genus.” *AbbVie*, 759 F.3d at 1300. Because polymorphic structures are highly unpredictable, two closely related species cannot represent the entire claimed genus. *See Noelle v. Lederman*, 355 F.3d 1343, 1350 (Fed. Cir. 2004) (“a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated”).

The district court faulted MSN for allegedly “not explain[ing] why these differences in physico-chemical properties and structure mean N-1 and N-2 are so different from other forms that they are unrepresentative.” Appx26. But MSN *did* explain why these differences matter, with unrebutted evidence that forms N-1 and N-2 are: (i) not predictive of other crystalline forms; (ii) different from other known crystalline forms; and (iii) may affect the manufacturability, performance, and quality of a drug product, which is why FDA guidance requires drugmakers to perform polymorph screening. Appx3556, Appx2553-2556; Appx2065 (919:24-920:3) (asked whether “differences in polymorphic form” can

result in “variable potency of a compound,” Dr. Trout agreed: “That’s a possibility. Yes.”); *supra* 12-14. The district court failed to address these significant differences.

Exelixis’ main response was that the physical properties MSN identified are “unclaimed” (Appx2692), but that is immaterial. “From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing.” *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963). That principle is especially relevant here, where the identity and only alleged utility for the claimed polymorphs lies in their unique and beneficial physico-chemical properties. *See* Appx127 (3:20-25), Appx129 (7:10-45). Moreover, in evaluating whether a patent discloses representative species, this Court has rejected the argument that “unclaimed structural features [] are legally irrelevant,” holding instead that a specification must “reflect the structural diversity of the claimed genus,” regardless of whether such features are claimed. *AbbVie*, 759 F.3d at 1298, 1301.

Thus, the Court should reverse the judgment below and hold that N-1 and N-2 are not sufficient representative species to support the claimed genus. At a minimum, the judgment should be vacated. Any

other result would unfairly punish and discourage generic companies like MSN that design around disclosed inventions in good faith, while encouraging gamesmanship by patentees like Exelixis that misuse continuation applications to ensnare products they never invented or disclosed.

II. The asserted claim of the '349 patent is invalid as obvious.

A. The district court clearly erred in declining to find that Regis followed the Brown process.

The district court's decision upholding claim 3 of the '349 patent turned on a single erroneous finding—that it was “not clear that the Regis process followed the Brown process.” Appx50 (cleaned up). Yet Exelixis *conceded* that Regis followed the Brown process, as confirmed by its own regulatory submissions and expert testimony. In finding that this undisputed fact “was not clear,” the district court clearly erred.

1. Regis followed the Brown process and inherently produced cabozantinib essentially free of the 1-1 impurity.

The trial record clearly and convincingly established that the Regis process used to manufacture the three Regis Batches followed the Brown process. Both MSN's expert, Dr. Lepore, and Exelixis' expert, Dr. Myerson, agreed that Regis followed the Brown process. They had to,

because reviewing the Brown process together with Exelixis' representations to FDA confirms the processes are identical.

Brown describes a detailed, "step-by-step" synthetic scheme for manufacturing cabozantinib (L)-malate. Appx5852. Accompanying the synthetic scheme is a comprehensive narrative description, spanning 17 paragraphs. Appx5852-5855. The synthetic route "is a five-step process with two side steps." Appx45. Brown discloses that its process can produce "substantially pure" cabozantinib (L)-malate—e.g., up to "about 100%" pure. Appx5851 (¶ 97); Appx1802 (269:5-16) (Lepore).

Regis followed the *exact* process Brown described. Appx1802-1803 (272:19-275:21) (Lepore) (the two schemes are "the same chemistry, same schemes," and the "very same process"). Dr. Myerson agreed that "[t]he language used by Exelixis in its IND to describe how the clinical material was manufactured [by Regis] is identical to Example 1 Brown." Appx2032 (786:2-7) (Myerson). There is no contrary evidence.

Regis manufactured three batches of cabozantinib (L)-malate: one batch (P163-183-1) "for GLP nonclinical safety studies" and two batches (P172-27-1 and P188-144-1) for a "proposed clinical trial." Appx3114-3115; Appx3219 (Table 1). Exelixis' IND explained that Regis used "the

same synthetic process in the production of drug substance for GLP non-clinical safety studies” as “used in the production of the drug substance ... for the proposed clinical trial.” Appx3115 (cleaned up). It was “undisputed that the three Regis batches all had lower than 100 ppm of the 1-1 impurity and thus met the ‘essentially free’ limitation.” Appx49.

While Exelixis’ IND noted “[s]ome processing and reagent changes were implemented for the GMP batch (Lot No. P172–27–1)” (Appx3115), Exelixis did not produce any underlying batch records evidencing such purported “changes.” Appx1874 (364:3-364:13) (Lepore); Appx2032 (787:8-22) (Myerson). Both experts concluded that Regis still followed the Brown process.

Dr. Lepore testified that any supposed “changes” mentioned in Exelixis’ IND would have been “extremely minor things” considering they were not identified as “deviations.” Appx1818 (335:19-336:2); Appx1874 (364:3-365:13); Appx1819 (338:14-19). A “deviation” occurs when a synthetic procedure is altered or process steps are added. Appx1808 (295:3-13) (Lepore). Because the purported Regis “changes” were not “deviations,” Dr. Lepore concluded that all three Regis batches followed the Brown process. Appx1874 (364:3-365:13).

Dr. Myerson reached the same conclusion but for a different reason. When cross-examined about “[t]he language used by Exelixis in its IND to describe how the clinical material was manufactured” and whether “Regis used exactly the method” of Brown, Dr. Myerson conceded Regis “followed Brown within the variability of Brown.” Appx2032 (785:21-786:5). Any such variability, however, is common to “all synthetic processes.” Appx2032 (785:21-786:7,787:5-7). For instance, both Brown and the ’349 patent use the word “approximately” when describing parameters that need not be precise. Appx2032 (787:2-788:16) (Myerson). Similarly, both Brown and the ’349 patent allow some variability, teaching that “it should be understood that many variations and modifications can be made while remaining within the spirit and scope or the invention” and that “changes and modifications can be practiced.” Appx5866 (¶00213); Appx92 (33:44-49). Since “synthetic processes are never exactly the same when done every time,” some variability will always exist. Appx2032 (785:21-786:7) (Myerson).

Nevertheless, Dr. Shah, a named inventor, explained that a synthetic process can nevertheless be “a consistent reproducible manufacturing process” with controls to synthesize cabozantinib (L)-malate

essentially free of the 1-1 impurity. Appx1936-1937 (615:9-616:10). Thus, even if Regis incorporated purported “processing and reagent changes,” Dr. Myerson agreed that Regis nonetheless “followed Brown within the variability of Brown.” Appx2032 (785:21-786:5).

2. The district court clearly erred in finding it was “not clear” whether the Regis process followed the Brown process, which was undisputed.

Exelixis conceded that the Regis “batches of cabozantinib (L)-malate [were] made with the Brown Process.” Appx2719. Exelixis had to do so because it “told FDA[] the Regis [] batches were made using the process disclosed in Brown.” Appx2720; *see also* Appx2763 (¶ 72) (“Exelixis told the FDA that both the Regis ... batches were made using the process disclosed in Brown.”); Appx2014 (716:18-24) (Dr. Myerson admitting “Exelixis in their submission to the FDA represented that the batches made by [Regis] were made according to A-2, which is the Brown process”). Despite Exelixis’ concession, the district court created its own argument to find “it was not clear that the Regis process followed the Brown process.” Appx50 (cleaned up). That was clear error.

First, the district court simply *assumed* that the IND’s discussion of “processing and reagent changes” referred to purported differences

between the Regis process and the Brown process, but that assumption is unsupported. Appx50. The IND never identifies specific “changes,” and Dr. Lepore’s unrebutted testimony showed there were no “changes” compared to the Brown process. Appx1874 (364:14-365:13). The IND submission mentions “[s]ome processing and reagent changes were implemented for the GMP batch (Lot No. P172-27-1),” but makes clear that “[t]he following description of the process is [] the current route and scale used in the production of the drug substance (Lot No. P172-27-1) at Regis” and that the “same synthetic process was used” for the other Regis batches. Appx3115. Thus, the IND’s “following description” necessarily includes the “changes [that] were implemented” for Lot No. P172-27-1. Appx3115.

That “following description” is the “step-by-step” narrative description that Dr. Lepore compared side-by-side with the Brown process. *Compare Appx3115-3118, with Appx5852-5855; Appx1802 (270:21-23), Appx1874 (364:3-13) (Lepore).* Dr. Lepore concluded: “According to that document, there were no changes” comparing the Regis process to the Brown process. Appx1818 (336:11-16); *see also* Appx1819 (337:22-338:3). Dr. Lepore “relied on the procedures that Exelixis provided to the FDA”

for the Regis process, compared it to the Brown process, and concluded the two “are virtually identical.” Appx1874 (364:3-365:13). Dr. Myerson agreed that the IND description of the Regis process was identical to the Brown process. Appx2032 (786:2-7).

Second, the district court found that “[t]he document Dr. Lepore relied on” did not paint the full picture because, “in *another document*, ... Regis stated there were some ‘processing and reagent changes’ to the synthetic route it had planned to follow.” Appx50 (citing Appx10786 and Appx3107). In reality, the two “document[s]” are the same,⁹ and neither was a statement by Regis. Appx2015 (720:4-7) (Myerson). Rather, the “regulatory document Exelixis prepared and submitted to the FDA” “represented that the batches made by the Regis process was made according to A-2, which is the Brown process.” Appx50; Appx2014 (716:18-24) (Myerson). Thus, the district court clearly erred by disregarding Exelixis’ representation to FDA because of a statement that Regis did not make.

As a result, the district court faulted Dr. Lepore for relying on “the information” “Exelixis put [] into its FDA document” instead of see[ing]

⁹ MSN introduced DTX-38 during Dr. Lepore’s direct examination, and Exelixis introduced the same document during his cross-examination as PTX-10. Appx1802 (271:5), Appx1818 (336:17).

what the changes were.” Appx50. But Exelixis never produced any underlying batch records with details of the purported “changes.” Appx1874 (364:3-364:13) (Lepore); Appx2032 (787:8-22) (Myerson).

Faulting Dr. Lepore for not knowing “what changes Regis made to the Brown process” (Appx50) is particularly unfair where Exelixis did not produce any evidence of the changes, and Dr. Lepore relied on the scientific details of the Regis process that Exelixis provided in a regulatory submission. Dr. Myerson agreed that Exelixis “represented” to FDA “that the batches made by [the Regis process] … were made according to [] the Brown process.” Appx2014 (716:18-24) (cleaned up).

If any contrary statements or records from Regis existed, they would have been reflected in Exelixis’ regulatory submissions. Dr. Shah, Exelixis’ corporate representative and named inventor, explained that Exelixis first reviewed “the data being provided from the contract manufacturer, who manufactures the product” (e.g., Regis), “scrutinized” “every line of the batch record” “line by line,” had “quality assurance” and “regulatory” teams that compared the submission “to the source data to make sure that it was accurate and correct,” and formally had “leadership sign off” on the submission. Appx1937 (617:16-618:11) (cleaned up).

Third, Dr. Lepore explained that even if Regis implemented “changes” to the Brown process, they were “extremely minor things,” given that “they’re not being called deviations.” Appx1819 (338:12-19). A “deviation” is “a bigger change”—i.e., an altered synthetic procedure or added steps. Appx1808 (295:3-13), Appx1819 (337:22–338:19) (Lepore). Because the “changes” in Exelixis’ IND are “not being called deviations,” they are “something very minor.” Appx1819 (337:22-338:19) (Lepore); *see also* Appx2032 (785:21-786:5) (Myerson testifying that Regis “followed Brown within the variability of Brown”).

Finally, the district court mistakenly found that the purported “processing and reagent changes” occurred for *all three* “Regis batches.” Appx46. At most, Exelixis’ IND indicates that any purported “changes” were “implemented for the GMP batch (Lot No. P172–27–1).” Appx3115. The two other Regis batches undisputedly followed the Brown process and resulted in cabozantinib (L)-malate that “met the ‘essentially free’ limitation.” Appx49. Even if the district court discounted the third batch, it was clear error to disregard all three Regis batches.

The only conclusion supported by the trial record is that Regis followed the Brown process for all three batches—or at least two—and the batches made with that process were essentially free of the 1-1 impurity.

B. The district court legally and clearly erred in its analysis of the underlying science supporting that the Brown process results in cabozantinib that is essentially free of the 1-1 impurity.

Apart from casting aside Regis' testing, the district court erred in analyzing evidence of “how the underlying science of the Brown process leads to an API essentially free of the 1-1 impurity.” Appx50. First, the district court legally erred by requiring MSN to prove that the Brown process inherently discloses more than the claimed invention requires—i.e., only that the formulation be “*essentially free*” (i.e., <200 ppm) of the 1-1 impurity. *Infra*, Part 1. Second, the district court legally and clearly erred in discounting MSN’s expert testimony, which did not merely address a POSA’s “expectation” but also corroborated Regis’ test results to confirm Brown’s inherent disclosure. *Infra*, Part 2.

1. Requiring MSN “to show that the Brown process does not form the 1-1 impurity through degradation” was too exacting of a standard.

The district court legally erred by demanding more from the Brown process than what the ’349 patent claims. The district court held “it is

MSN's burden [] to show that the Brown process does not form the 1-1 impurity through degradation." Appx51. But claim 3 of the '349 patent allows up to 200 ppm of the 1-1 impurity.

Inherency in the obviousness context requires only proof that "*the limitation at issue* necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Hospira*, 946 F.3d at 1329. MSN showed that Brown inherently met the "essentially free" limitation with Regis' testing. While the district court further required "expert testimony of the underlying scientific principles" (Appx49), at most, that testimony only had to show that the Brown process produces cabozantinib API essentially free of the 1-1 impurity, not that the impurity "does not form" at all (Appx51).

This Court addressed a similar issue in *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005). There, the prior art taught PHC *anhydride*, and the claim "cover[ed] PHC *hemihydrate* without further limitation." *Id.* 1341. The defendant "asserted that [the prior art] process of making PHC anhydride inherently resulted in trace amounts of the hemihydrate," rendering the claim invalid. *Id.* The district court found no inherency because the defendant had not shown "it

was impossible to make pure PHC anhydrate.” This Court held that “the district court erred in requiring … this standard of proof, which is too exacting.” *Id.* at 1343. The defendant “did not need to prove that it was impossible to make PHC anhydrate … that contained no PHC hemihydrate, but merely that ‘the disclosure [of the prior art] is sufficient to show that the natural result flowing from the operation as taught [in the prior art] would result in’ the claimed product.” *Id.* (quotation omitted).

So too here. MSN does not have a “burden [] to show that the Brown process does not form the 1-1 impurity through degradation,” as the district court erroneously found. Appx51. MSN’s only burden was to show that formulating cabozantinib using the Brown process resulted in material “essentially free” of the 1-1 impurity. MSN did so. Thus, even if “the 1-1 impurity could have formed as a degradation product,” as the district court speculated (Appx50), that is irrelevant so long as it does not form in an amount above 200 ppm in the final product.

2. The district court legally and clearly erred by finding that the underlying scientific evidence did not support a finding of inherency.

The district court also found “MSN’s expert testimony … does not meet the clear and convincing evidence standard” because “what a POSA

would have expected is not sufficient to show inherency.” Appx50-51.

The district court both legally and clearly erred.

First, the district court legally erred in discounting undisputed evidence that a POSA would have expected the Brown process to result in cabozantinib essentially free of the 1-1 impurity. MSN did not rely on that testimony standing alone but as scientific corroboration for Regis’ testing, which confirmed the inherent result of the Brown process. MSN’s reliance on expert testimony showing a POSA’s expectation to corroborate test results is consistent with this Court’s caselaw. For example, this Court in *Santarus* held that where there was “no dispute that the [claimed] blood serum concentrations [we]re *expected* in light of the dosages,” the limitation was “an inherent property of the formulation.” *Santarus*, 694 F.3d at 1354 (Fed. Cir. 2012); *see also PAR*, 773 F.3d at 1195-96 (“Importantly, though, neither party disputed that the blood serum concentrations claimed in *Santarus* were *expected* in light of the dosages disclosed in the prior art.”).

Regardless, the expert testimony went beyond merely articulating an “expectation.” Dr. Lepore unequivocally explained that “the Brown process *would always produce* an API with less than 200 ppm impurity.”

Appx50 (n.14); Appx1809 (299:10-18). Likewise, Dr. Lepore opined that a POSA following the Brown process would have “*necessarily and inherently obtained* cabozantinib (L)-malate that is essentially free of the 1-1 impurity.” Appx1874 (366:14-18). This testimony does not merely state “what a POSA would have expected” (Appx50), but explicitly opines on inherency, as supported by Regis’ testing.

Second, the district court clearly erred in finding no inherency based on the notion “that the 1-1 impurity could have formed as a degradation product during the Brown process.” Appx51. Dr. MacMillan explained that “a POSA would not expect any 1-1 impurity to be left at the end of Brown, because each of the five steps of Brown has a purification component and the reagents added through the process could purge the impurity.” Appx50 (n.14). Dr. Myerson agreed “there are multiple purification processes and other steps with purification processes” in the Brown process, such that “at the end of the fifth step, we would not expect any significant amount of 1-1 to carry through.” Appx2013 (709:5-14). Instead, the POSA “would expect [the 1-1 impurity] to be de minimis” and would not expect “the 1-1 impurity forms as a degradation process during synthesis.” Appx2013 (709:5-19) (Myerson).

Indeed, in rejecting an alternative obviousness argument that a POSA would have been motivated to control for the 1-1 impurity, the district court correctly found that a “POSA would expect that there is, at most, a de minimis amount of impurity left at the end of the Brown process.” Appx46; *see also* Appx53 (“a POSA would not expect that the 1-1 impurity would be present by the end of the Brown process”); Appx2013 (709:5-19) (Myerson testifying that a POSA would *not* expect “the 1-1 impurity forms as a degradation process during synthesis”).

While the district court credited testimony from Dr. Myerson about a “1-3 [intermediary]” that could supposedly decompose into the 1-1 impurity (Appx51), that testimony was about Exelixis’ previous *A-1* process—not the Brown process Exelixis labeled “*A-2*.¹” Appx1956 (693:11-12). Likewise, the district court erroneously relied on Dr. Myerson’s testimony about a subsequent *B-2* process. *See* Appx51 (citing Appx1950 (671:2-20)). Neither citation is relevant. At best, the remaining citations indicate that *some* 1-1 impurity could form, but there is no evidence suggesting that *more than 200 ppm* of the impurity formed, as required to take the product outside the scope of the claim. *See* Appx51 (citing Appx1925 (569:16-25) (Wilson); Appx1933 (600:8-601:4) (Shah)).

There was no genuine dispute that the claimed purity (i.e., the “essentially free” limitation) was both achieved (by Regis’ testing) and expected based on the underlying science of Brown’s purification steps. Appx46, Appx53. In requiring more to prove inherency, the district court erred. And because the “essentially free” limitation was the only disputed limitation, this Court should reverse the judgment of nonobviousness for claim 3 of the ’349 patent.

CONCLUSION AND RELIEF SOUGHT

The Court should reverse the district court’s judgment that the asserted claims are not invalid. The Court should hold that the malate salt patents’ asserted claims are invalid for lacking written description, and the ’349 patent’s asserted claim is invalid for obviousness. Alternatively, the Court should at least vacate the judgment against MSN’s invalidity defenses and remand for the district court to consider those defenses under the correct legal standards.

Respectfully submitted,

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April 1, 2025

ADDENDUM

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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

EXELIXIS, INC.,

Plaintiff,

v.

MSN LABORATORIES PRIVATE
LIMITED and MSN
PHARMACEUTICALS, INC.,

Defendants.

Civil Action No. 22-228-RGA
(Consolidated)

TRIAL OPINION

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October 15, 2024



ANDREWS, U.S. DISTRICT JUDGE:

Exelixis, Inc. brought this patent infringement action under 35 U.S.C. §§ 271(a)–(c) and/or (e)(2) and pursuant to the Hatch-Waxman Act codified at 21 U.S.C. § 355 against MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc. (“MSN”). (D.I. 1 ¶¶ 1–2, D.I. 124 ¶ 1). I held a four-day bench trial from October 23 to October 26, 2023.

The asserted patents fall into two groups. The first group consists only of U.S. Patent No. 11,298,349 (the “‘349 patent”). Exelixis asserted Claim 3 of the ‘349 patent. The parties dispute whether MSN infringed Claim 3 of the ‘349 patent. (D.I. 124 ¶ 6). The parties dispute whether Claim 3 of the ‘349 patent is invalid as obvious. (*Id.*).

The second group consists of U.S. Patent Nos. 11,091,439 (the “‘439 patent”), 11,091,440 (the “‘440 patent”), and 11,098,015 (the “‘015 patent”). This group is called the Malate Salt Patents; they share an identical specification. (*Id.* ¶ 33). The claims at issue are Claim 4 of the ‘439 patent, Claim 3 of the ‘440 patent, and Claim 2 of the ‘015 patent. (*Id.* ¶ 6). MSN stipulated to the infringement of the asserted claims of the Malate Salt Patents. (D.I. 23). The parties dispute whether the asserted claims of the Malate Salt Patents are invalid for lack of written description and obviousness-type double patenting.

For the following reasons, I find Claim 3 of the ‘349 patent not infringed and not invalid. I find the asserted claims of the Malate Salt Patents not invalid.

I. BACKGROUND

MSN submitted Abbreviated New Drug Application (“ANDA”) No. 213878 to the U.S. Food and Drug Administration (“FDA”), seeking approval to manufacture and sell a generic version of Cabometyx, a cancer drug made by Exelixis (the “MSN ANDA Product”). (D.I. 1 ¶ 1).

Exelixis brought a complaint, alleging MSN infringed the Malate Salt Patents. (D.I. 1 ¶¶ 28–56). Exelixis had filed a separate action against MSN, alleging infringement of the '349 patent. (D.I. 34)¹. The two actions are consolidated into the present case. (*Id.*).

The asserted Malate Salt Patent claims require a cabozantinib malate salt that is crystalline. ('439 patent at 32:22–24, 32:28–36; '440 patent at 32:16–21; '015 patent at 32:11–16). The '349 patent is directed to a pharmaceutical composition of cabozantinib (L)-malate that includes certain classes of excipients and is free of a harmful genotoxic impurity. ('349 patent at 34:30–51).

Exelixis sells Cabometyx and Cometriq. Cabometyx is indicated for the treatment of kidney cancer, liver cancer, and differentiated thyroid cancer. (D.I. 124-1 at 9 of 314). Exelixis markets capsules comprising cabozantinib (S)-malate² in the United States under the trade name Cometriq. (*Id.*). Cometriq is indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer. (*Id.* at 10 of 314). The active pharmaceutical ingredient (“API”) in Cabometyx and Cometriq is the (L)-malate salt of cabozantinib. (*Id.* at 7–8 of 314).

The Malate Salt Patents and the '349 patent have been listed in connection with Cabometyx in the FDA's Orange Book. (*Id.* at 10 of 314).³

II. LEGAL STANDARD

A. Infringement

A patent is directly infringed when a person “without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any

¹ The complaint for the '349 patent is filed in case number 22-945. The complaint was filed before the actions were consolidated into the present case.

² Dr. Shah testified that (S)-malate and (L)-malate are the same type of salt. The (S) and (L) refer to different naming conventions. (Tr. 589:9–13).

patented invention during the term of the patent.” 35 U.S.C. § 271(a). Determining infringement is a two-step analysis. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff’d*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *Id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *Id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). The patent owner bears the burden of proving infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab’ys Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

In a Hatch-Waxman case, the plaintiff’s infringement claim is based on the accused infringer’s future conduct, rather than past acts of infringement. Under § 271(e)(2), the “infringement inquiry . . . is focused on the product that is likely to be sold following FDA approval.” *Abbott Lab’ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). “Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA’s description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry.” *Id.*

“Whoever actively induces infringement of a patent shall be liable as an infringer.” 35 U.S.C. § 271(b). To prevail on a claim of induced infringement, the plaintiff must show (1) “that there has been direct infringement,” and (2) “that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another’s infringement.” *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018) (cleaned up). In a Hatch-Waxman case, a plaintiff “can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted]

claim].” *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018).

B. Written Description

The written description requirement of 35 U.S.C. § 112 requires that the specification “clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original). “In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Id.* “When determining whether a specification contains adequate written description, one must make an ‘objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.’” *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (quoting *Ariad*, 598 F.3d at 1351).

The written description inquiry is a question of fact. *Ariad*, 598 F.3d at 1351. “A party must prove invalidity for lack of written description by clear and convincing evidence.” *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 682 (Fed. Cir. 2015).

C. Obviousness

A patent claim is invalid as obvious under 35 U.S.C. § 103 “if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). “As patents are presumed valid, a [defendant] bears the burden of proving invalidity by clear and convincing evidence.” *Shire, LLC v. Amneal*

Pharms., LLC, 802 F.3d 1301, 1306 (Fed. Cir. 2015) (internal citations and quotation marks omitted). “Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.” *KSR*, 550 U.S. at 406 (internal citation and quotation marks omitted).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a “check against hindsight bias.” See *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1078–79 (Fed. Cir. 2012). “Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.” *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

D. Obviousness-Type Double Patenting

Generally, an obviousness-type double patenting analysis entails two steps. First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences. *Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999). Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct. *Id.* at 1327. A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obviousness-type double patenting. *In re Berg*, 140 F.3d 1428, 1431 (Fed. Cir. 1998). A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim. *Eli Lilly & Co. v. Barr Lab'ys, Inc.*, 251 F.3d 955, 968

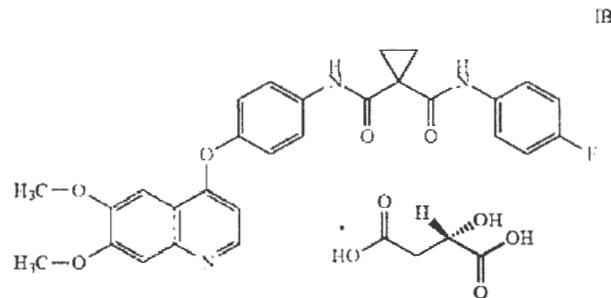
(Fed. Cir. 2001). Objective indicia (that is, secondary considerations) of non-obviousness must be considered in an obviousness-type double patenting analysis. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1381 (Fed. Cir. 2012).

III. INFRINGEMENT

A. The Asserted Claim

The parties dispute whether MSN's ANDA Products infringe Claim 3 of the '349 patent. Claim 3 recites:

A pharmaceutical composition for oral administration comprising Compound IB;



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and;
wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.

('349 patent at 34:30–51).⁴

B. Findings of Fact

1. A glidant is a material that improves the flow of a drug powder mixture. (Tr. 60:2–4, 82:9–11, 230:16–19).⁵

⁴ The parties refer to “6,7-dimethoxy-quinoline-4-ol” as the “1-1 impurity.” I will also refer to it as such.

⁵ “Tr.” refers to the trial transcript. (D.I. 161, 162, 163, 164). It is consecutively paginated.

2. A diluent can affect the flow properties of a mixture. (Tr. 194:21–195:6, 227:10–228:3).
3. An excipient can have multiple functions. (Tr. 77:3–8, 179:25–180:4, 247:12–13). An excipient can be both a glidant and a diluent. (Tr. 77:3–8, 93:2–6, 247:12–22).
4. Neither the claims nor the specification of the '349 patent state that a glidant must improve flow through specific mechanisms. ('349 patent; Tr. 116:17–25).
5. Remington and Swarbrick are two authorities on pharmaceutical compositions cited in the '349 patent specification. ('349 patent at 20:40–49). Remington defines glidant as “a substance that improves the flow characteristics of a powder mixture.” (PTX-572A at 13 of 48). Swarbrick states that “glidant excipients improve the flow characteristics of tablet granulations (and capsule powder blends).” (PTX-394 at 26 of 69).
6. The cabozantinib (L)-malate API exhibits poor flow properties. (Tr. 60:16–24, 89:5–16; DTX-215 at 34 of 116).
7. GRASTAR is a starch derivative known as granulated corn starch. (Tr. 86:5–11, 96:6–7).
8. Glidants are typically added after wet granulation, during the pre-lubrication step. (Tr. 83:5–84:3, 228:19–23). MSN adds GRASTAR in its ANDA products during the pre-lubrication step, just prior to compression. (Tr. 86:12–16). Exelixis adds a glidant during the pre-lubrication step after wet granulation in manufacturing Cabometyx. (Tr. 609:15–21, 610:10–23). MSN adds GRASTAR in its manufacturing process at the same step that glidants are typically added. (Tr. 104:10–17, DTX-215 at 97–98 of 116).
9. Disintegrants, fillers, and other ingredients can also be added at the pre-lubrication stage of manufacturing. (Tr. 142:9–22, 228:14–229:10).
10. MSN adds GRASTAR at a concentration of 9.71% of the total drug mixture. (Tr. 105:18–21, 201:21–22). The scientific literature discloses that the typical concentration range for a starch glidant is between 1 and 10.0%. (Tr. 97:24–98:7, 232:24–233:11). 9.71% is also consistent with what the scientific literature reports for potential use of granulated corn starch as a filler in pharmaceutical compositions. (Tr. 201:21–202:4, DTX-275 at 754, 790 of 945).
11. MSN submitted a Pharmaceutical Development Report (“PDR”) to the FDA. (DTX-215). In the Initial Risk Assessment portion of the PDR, MSN includes a table of different drug substances. (DTX-215 at 36 of 116). MSN states “Granulated Corn Starch is used as a diluent in minimal concentration and it enhances the flowability of the granules.” (*Id.*). This type of table is usually prepared after the core formulation is identified. (Tr. 91:9–25). This assessment is usually performed before formulation development starts to direct and prioritize evaluating a formulation. (Tr. 227:2–9).

12. To justify its manufacturing process selection, MSN told the FDA in its PDR that the process of choice was wet granulation over direct compression after stating it is evident the API exhibits poor flow properties. (DTX-215 at 34 of 116).
13. In the Formula Optimization Section of PDR, MSN states, “The level of Granulated [C]orn Starch plays an important role in flow characteristics.” (DTX-215 at 58 of 116).
14. In MSN’s Justification for Microbial Method Validation, MSN wrote “Starch are used in pharmaceutical industry for a wide variety of reasons, such as an excipient in tablet and capsule as a diluent, as a glidant or as binder.” (PTX-724 at 2 of 3, Tr. 101:3–7).
15. GРАSTAR’s manufacturer conducted testing on GРАSTAR which showed that GРАSTAR has better flowability than Japanese Corn Starch. (Tr. 119:25–120:15). The testing showed that GРАSTAR improved flowability of fenofibrate, another drug substance, more than Japanese Corn Starch did. (Tr. 119:15–121:23). GРАSTAR’s manufacturer says that GРАSTAR has excellent oral disintegration properties, and lists filler as one of the functions of GРАSTAR. (Tr. 164:1–18). The manufacturer does not identify GРАSTAR as a glidant in any literature. (Tr. 164:16–18).
16. MSN told the FDA that GРАSTAR improves flow. (FOF ¶¶ 12–15).
17. The changes to MSN’s excipients during formulation development, including the substitution of maize starch B with GРАSTAR, were focused on the disintegration and dissolution properties of its tablets. (Tr. 210:1–211:16, 212:1–5).
18. Whether GРАSTAR acts as a glidant in a particular pharmaceutical composition depends on the pharmaceutical composition. Dr. Koleng concedes that both unmodified and pregelatinized starches can serve as fillers in pharmaceutical formulations without also being glidants. (Tr. 155:7–156:15). Dr. Nithyanandam testified that whether GРАSTAR will actually improve flow depends on the specific formulation in which GРАSTAR is used. (Tr. 61:17–62:9).
19. The literature identifies that granulated corn starch is a commonly used glidant. (Tr. 95:13–96:7).
20. Swarbrick identifies starch and its derivatives as commonly used glidants (Tr. 95:13–96:7). Granulated corn starch is a starch derivative. (*Id.*).
21. The Lachman reference states that starch and starch 1500, which is pregelatinized corn starch, are “commonly used glidants.” (PTX-553A at 197–98 of 611; Tr. 96:11–97:19). Dr. Koleng testified that granulated corn starch is pregelatinized corn starch. (Tr. 97:11–19).

22. MSN's lab notebook data that purportedly shows GRASTAR does not improve flow is unreliable. (DTX-196). The Hausner Ratio and Carr Index for the GRASTAR batch were incorrectly calculated from the recorded bulk density and "tapped density."⁶ (Tr. 139:1–141:9). It is unclear if the error was in the recorded bulk density and tapped density or the calculated Hausner Ratio and Carr Index. (Tr. 107:12–18).

23. MSN's ANDA does not infringe Claim 3 of the '349 patent.

C. Conclusions of Law

1. Definition of Glidant

The parties agree that MSN's ANDA Products meet all the claim limitations of Claim 3 other than "comprising . . . one or more glidants." (D.I. 149-1 ¶¶ 65–70; '349 patent at 34:30–51). The only disputed issue, therefore, is whether MSN's ANDA Products include a glidant such that MSN's ANDA Products infringe Claim 3 of the '349 patent.

The parties dispute the definition of a glidant. Exelixis defines glidant as "a material that improves the flow of a drug powder mixture." (D.I. 167 at 5). MSN defines glidant as a material that improves flow of a powder blend through five specific mechanisms: "(1) coating/adherence; (2) adsorbing fine particles; (3) reducing electrostatic forces; (4) adsorbing environmental gases; and (5) reducing van der Waals forces." (D.I. 173 at 4). These are the only two definitions the parties proposed.

The parties did not ask me to construe glidant, or any term in the '349 patent. (D.I. 53). Therefore, "glidant" is given its plain and ordinary meaning. "[T]he 'ordinary meaning' of a

⁶ "Tapped density" is not defined in the trial record. (D.I. 183 at 1). After I issued an oral order asking the parties if "tapped density" was defined in the record, MSN asked me to take judicial notice of the US Pharmacopeia's definitions of "tapped density" and "bulk density." (D.I. 184 at 1). I decline to do so. It is in my discretion whether to reopen the record. *Zenith Radio Corp. v. Hazeltine Rsch.*, 401 U.S. 321, 331 (1971). The definitions may be subject to "reasonable dispute" and, indeed, Exelixis has opposed MSN's request. FED. R. EVID. 201(b); (D.I. 185 at 1). The definitions are not material to this case or my decision. For these reasons, I exercise my discretion to decline to reopen the record and take judicial notice of the definitions.

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claim term is its meaning to the ordinary artisan after reading the entire patent.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1321 (Fed. Cir. 2005). “[I]ntrinsic evidence is the most significant source of the legally operative meaning of disputed claim language.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

I agree with Exelixis that a glidant is “a material that improves the flow of a drug powder mixture.” As Exelixis argues, neither the claims nor specification of the ’349 patent state that a glidant must improve flow through specific mechanisms. Dr. Koleng testified that after reviewing the patent, he could not find any “mechanism requirement” for something to be a glidant. (Tr. 116:17–19). Dr. Koleng further testified that neither Claim 3 of the ’349 patent nor its specification references a particular mechanism for a glidant. (Tr. 116:20–25). The intrinsic evidence supports that the definition of a glidant does not need to include the mechanism of action.

Exelixis also cites extrinsic evidence to support its definition. The Remington and Swarbrick references define a glidant as a substance or excipient that improves flow of a powder mixture or tablet granulations. (Tr. 231:14–232:20). Neither reference states that an excipient is a glidant only if it functions through specified mechanisms. Furthermore, Dr. Donovan, Dr. Koleng, and Mr. Nithiyanandam all testified that a glidant is a chemical that improves the flow characteristics of a powder blend. (Tr. 82:9–11, 230:16–19, 60:2–4).

MSN presents only extrinsic evidence to support its contention that the definition of a glidant includes a mechanism of action. But extrinsic evidence is disfavored when intrinsic evidence is available. *Phillips*, 415 F.3d at 1317. (“[W]hile extrinsic evidence can shed useful light on the relevant art, we have explained that it is less significant than the intrinsic record in determining the legally operative meaning of claim language.” (internal citations and quotations

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omitted)). I do not understand the Lachman reference to disclose that a glidant must use a particular mechanism. The Lachman reference states only that “the mechanisms of action of a glidant have been hypothesized,” then list several mechanisms. (PTX-553 at 136 of 611). The only reference MSN cites that indicates glidants function through specific mechanisms is the Swarbrick reference, which states, “Glidant excipients are usually added to improve flowability of powder blends and granulations through one or more of several proposed physical mechanisms [listing mechanisms].” (PTX-394 at 33–34 of 69). But Swarbrick earlier defines glidant without reference to mechanisms. (*Id.* at 26 of 69). Swarbrick’s characterization of the mechanisms as “proposed” indicates that these mechanisms might not be the complete list of how a glidant works. MSN’s extrinsic evidence does not persuade me that the definition of a glidant should include specific mechanisms of action.

MSN argues that a POSA would not find every material that improves flow to be a glidant. (D.I. 173 at 15). Dr. Donovan testified that a POSA would not consider every excipient that has any positive impact on powder flow to be a glidant. (Tr. 198:24–199:3, 254:19–255:2). But in defining glidant, I must consider the extrinsic evidence in the context of the intrinsic evidence. *Phillips*, 415 F.3d at 1319. Because the patent does not limit the definition of a glidant to certain mechanisms, the intrinsic evidence suggests the definition of glidant is broader than the definition MSN argues the extrinsic evidence advances. “[E]xtrinsic evidence . . . may not be used to vary, contradict, expand, or limit the claim language from how it is defined, even implicitly, in the specification.” *Dow Chem. Co. v. Sumitomo Chem. Co.*, 257 F.3d 1364, 1373 (Fed. Cir. 2001). I am not persuaded by Dr. Donovan’s testimony because the intrinsic evidence never mentions that glidants use particular mechanisms. I agree with Dr. Koleng, who testified that any material that improves flow is a glidant. (Tr. 128:21–24).

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MSN argues that a diluent can affect the flow properties of a mixture. I agree, but I do not think the argument helps MSN. An excipient can have multiple functions. (Tr. 77:3–8, 179:25–180:4, 247:12–13). For example, an excipient can be both a glidant and a diluent. (Tr. 77:3–8, 93:2–6, 247:12–22). If an excipient is a diluent, that does not mean it is not also a glidant.

MSN argues that defining glidant as any material that improves flow is too broad because then “at least half—if not all” excipients that are added to a poorly flowing mixture would be a glidant. (D.I. 173 at 17). MSN does not cite to any evidence in the record in support of the “at least half—if not all” argument. (*Id.*). I therefore disregard this argument.

I define glidant as “a material that improves the flow of a drug powder mixture.”

2. Direct Infringement

With this definition of glidant in mind, I now turn to the evidence presented regarding whether the ANDA product has a glidant. The dispute concerns GRASTAR, which is added to the ANDA product at the pre-lubrication step. (FOF ¶ 8). Exelixis argues GRASTAR is a glidant, whereas MSN argues GRASTAR is a diluent, not a glidant. (D.I. 167 at 6, D.I. 173 at 11–12). Because an excipient can be both a glidant and a diluent, I do not consider persuasive MSN’s arguments that GRASTAR is a diluent. And since I have defined glidant as “a material that improves the flow of a drug powder mixture,” I focus my analysis on arguments relating to whether GRASTAR improves flow of the drug powder mixture.

MSN presented data from a laboratory notebook that purportedly shows that GRASTAR does not improve flow. (D.I. 173 at 8). MSN argues that therefore, GRASTAR is not a glidant. (*Id.*). The experiment in the laboratory notebook tested which of two different formulations of the cabozantinib API had better flow. (DTX-196 at 46, 84 of 175). The two formulations were the same, except that one formulation (Batch 252/023) included 30 mg/unit of GRASTAR and

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the other (Batch 252/044) included 30 mg/unit of unmodified corn starch. (Tr. 134:11–21, 135:19–136:6, 210:1–21). The notebook contained experimentally determined values for bulk density and tapped density for each batch. (Tr. 135:15–137:1). From the bulk density and tapped density, the Hausner Ratio and Carr Index, two numerical values that characterize powder flow, were calculated. (*Id.*). I disregard this data because, for two reasons, I find it unreliable.

First, there was an error in the laboratory notebook that makes the data unreliable. Dr. Koleng testified that the Hausner Ratio and Carr Index for the GRASTAR batch were incorrectly calculated from the recorded bulk density and tapped density. (Tr. 139:1–141:4). The parties agree that the correctly calculated Hausner Ratio and Carr Index, from the recorded bulk density and tapped density, would indicate that GRASTAR decreases flow. (Tr. 139:19–140:9; D.I. 173 at 10). MSN would have me disregard the computational error and use the correctly calculated Hausner ratio and Carr Index to conclude that GRASTAR does not improve the flow of the cabozantinib API. I agree, however, with Exelixis that the error puts into question the validity of the whole experiment. It is unclear whether the recorded bulk density and tapped density are correct, or whether the Hausner Ratio and Carr Index were correct but the bulk and tapped density were recorded incorrectly. While MSN assumes the recorded densities are correct, neither party introduced evidence of the origin of the error. Dr. Koleng disregarded the totality of the laboratory notebook because he found “[t]he source of th[e] disparity could not be identified within the context of the documents provided.” (Tr. 107:16–18). I agree that the lab notebook should not be taken into consideration. *See Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 2018 WL 6011697, at *9 (D. Del. Nov. 15, 2018) (giving little weight to a set of results because the laboratory notebook documenting the test offered insufficient detail); *In re Johnson & Johnson Talcum Powder Prod. Mktg., Sales Pracs. & Prod. Litig.*, 509 F. Supp. 3d 116, 147

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(D.N.J. 2020) (stating that computation errors in a lab notebook may impact the weight that a factfinder gives to the lab notebook).

Second, I do not think the lab notebook shows what it sets out to show: that GRASTAR does not improve flow and therefore is not a glidant. At trial, I asked counsel for MSN what is shown by comparing the flow of two formulations with two purported glidants. (Tr. 1046:3–7). I thought then, as I do now, that the relevant testing would have been comparing the flow properties of a formulation with GRASTAR and a formulation without GRASTAR. (Tr. 1046:15–17). The only information to take away from the lab notebook, if I accept the corrected Hausner ratio and Carr Index, is that corn starch improves flow more than GRASTAR does. (Tr. 1046:3–7). But this does not eliminate the possibility that GRASTAR is also a glidant, albeit a worse one than unmodified corn starch.

MSN argues that Dr. Koleng relied on the MSN lab notebook to opine that GRASTAR is a glidant when he thought the batch with GRASTAR had a lower Hausner Ratio and Carr Index, thus indicating GRASTAR improved flow. (D.I. 173 at 11). MSN argues that Dr. Koleng cannot now disregard the lab notebook data he was willing to use when it supported his conclusion that GRASTAR is a glidant. (*Id.*). But Dr. Koleng was relying on the lab notebook only at the time when he thought the underlying data was accurate. (Tr. 135:1–18). When notified that there were errors, Dr. Koleng disregarded the lab notebook. (Tr. 107:16–18).

Exelixis presents two arguments for why GRASTAR is a glidant. First, Exelixis argues that GRASTAR is a glidant because it is added at the same time and concentration (9.71%) that a glidant would be added in manufacturing. (D.I. 167 at 7–8). GRASTAR is added at the pre-lubrication step. (*Id.*). The literature confirms that this is the step when glidants are added and is the same step when Exelixis adds its glidant in its manufacturing process. (Tr. 83:23–84:3). But

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Dr. Donovan and Dr. Koleng testified that other excipients, such as disintegrants and fillers, can also be added at the pre-lubrication step. (Tr. 142:9–22, 228:14–229:10). Dr. Donovan testified that a concentration of GRASTAR of 9.71% is consistent with the use of GRASTAR as a filler. (Tr. 201:21–202:4). Because MSN has shown that other excipients could be added at the pre-lubrication step and at a concentration of 9.71%, this evidence does not show that GRASTAR is a glidant.

Second, Exelixis cites several statements that GRASTAR improves flow to argue it is a glidant.

- Exelixis argues that because MSN told the FDA that GRASTAR improves flow, it is a glidant. (D.I. 167 at 8). Specifically, MSN told the FDA in its Initial Risk Assessment that granulated corn starch enhances the flowability of the granules. MSN argues that this statement is out of context. (*Id.* at 9). Dr. Donovan testified that the Initial Risk Assessment is usually performed before formulation development starts to direct and prioritize evaluating a formulation. (Tr. 227:2–9). Therefore, MSN argues, there is no experimental evidence that GRASTAR improved flow in the final formulation. (D.I. 173 at 7). Dr. Nithiyanandam testified that this was written based on the scientific literature before formulation development trials started. (Tr. 61:17–62:2). Dr. Nithiyanandam also testified that whether GRASTAR will actually improve flow depends on the specific formulation in which GRASTAR is used. (Tr. 62:4–9). I am persuaded by Dr. Nithiyanandam’s testimony and agree that MSN’s statement to the FDA does not establish that GRASTAR improves flow in MSN’s formulation.

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- MSN told the FDA that the level of granulated corn starch plays an important role in flow characteristics. (D.I. 167 at 8–9). Dr. Nithiyanandam testified that the context of this statement was testing dissolution profiles of cabozantinib tablets with different weight percentages of granulated corn starch. (Tr. 63:15–64:5). Dr. Nithiyanandam explained that the statement was based more on the dissolution profile of granulated corn starch rather than the flow properties of granulated corn starch. (*Id.*). Dr. Donovan explained that no flow testing was conducted in support of the statement. (Tr. 214:25–215:8). I am persuaded that the statement does not establish that GRASTAR improves flow in MSN’s formulation.
- Exelixis cites Swarbrick and Lachman as identifying granulated corn starch as a commonly used glidant. (D.I. 167 at 11).
- Exelixis points to testing by GRASTAR’s manufacturer. (D.I. 167 at 10). The manufacturer concluded that GRASTAR has better flowability than Japanese corn starch when both were tested using fenofibrate as the drug substance. (*Id.*).
- Dr. Donovan testified that GRASTAR would “be expected, even before experiments, to potentially enhance the flowability of the granules.” (Tr. 237:7–9).
- Dr. Donovan testified that GRASTAR “had good flow properties so it would be expected that the addition of GRASTAR could improve the flow properties.” (Tr. 217:21–23).

The statements show that GRASTAR can be used as a glidant, because they show that GRASTAR does improve flow in some contexts. For example, GRASTAR improves the flow of fenofibrate. (Tr. 120:12–15). And I am persuaded that the literature explains that GRASTAR is a

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commonly used glidant. But there is no evidence that GRASTAR improves the flow of the API in this formulation. A glidant is “a material that improves the flow of a drug powder mixture.” But if GRASTAR is not improving the flow of this powder mixture, then it is not acting as a glidant in MSN’s ANDA Product. Whether GRASTAR acts as a glidant in a particular pharmaceutical composition depends on the pharmaceutical composition.

The statements Exelixis cites, including the statements made to the FDA, do not pertain to MSN’s pharmaceutical composition. The only evidence somewhat relating to MSN’s pharmaceutical composition is that Dr. Donovan testified that GRASTAR would “be expected, even before experiments, to *potentially* enhance the flowability of the granules.” (Tr. 237:7–9) (emphasis added).

Exelixis argues that it does not need to present direct evidence of testing to prove infringement. (D.I. 178 at 5). I take Exelixis to be arguing that Exelixis does not need to present experimental evidence that GRASTAR improved flow in MSN’s ANDA product. Exelixis cites to *C R Bard Inc. v. AngioDynamics, Inc.*, 979 F.3d 1372, 1379 (Fed. Cir. 2020). I find *Bard* instructive. There, the Federal Circuit held that, on a motion for judgment as a matter of law, the plaintiff did not need to test the defendant’s product to show that it infringed but could rely on the defendant’s “statements to the FDA regarding the product’s capabilities.” *Id.* at 1378–79. The Federal Circuit held that “statements regarding the capabilities of [the defendant’s] own product constituted substantial evidence of those capabilities.” *Id.* at 1379. To be sure, the standard for JMOL, substantial evidence, is harder to meet than the preponderance standard for infringement. But here, the evidence is slight. MSN did not present statements to the FDA regarding its product’s capabilities. I cannot find that Exelixis met its burden based on Dr. Donovan’s one equivocal statement about “potential” enhancement.

Exelixis has not met its burden to show there is a glidant in MSN's ANDA products, because it did not show by a preponderance of the evidence that GRASTAR is improving flow in MSN's ANDA products. I find MSN did not directly infringe the '349 patent.

3. Induced Infringement

Because I have found that Exelixis did not prove direct infringement of the '349 patent, it follows that Exelixis did not prove any indirect infringement of the '349 patent. *See Meyer Intell. Props. Ltd. v. Bodum, Inc.*, 690 F.3d 1354, 1366 (Fed. Cir. 2012) ("It is well-established that a finding of direct infringement is a prerequisite to a finding of inducement.").

IV. INVALIDITY

The parties dispute whether Claim 3 of the '349 patent is invalid for obviousness.

The parties dispute whether the asserted claims of the Malate Salt Patents are invalid for written description and obviousness-type double patenting. The Malate Salt Patents share a common specification. (D.I. 124 ¶ 33). The three asserted claims of the Malate Salt Patents (and the claims from which they depend) are reproduced below:

1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is crystalline.
('439 patent at 32:22–24).
3. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is the (L)-malate salt or (D)-malate salt.
('439 patent at 32:29–32).
4. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (L)-malate salt.
('439 patent at 32:33–36).

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3. A pharmaceutical composition comprising the N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or (D)-malate salt and wherein said salt is crystalline; and a pharmaceutically acceptable excipient.

('440 patent at 32:16–21).

1. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, and wherein said salt is crystalline.

('015 patent at 32:5–10).

2. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, said salt is crystalline, and said cancer is kidney cancer.

('015 patent at 32:11–16).

V. WRITTEN DESCRIPTION

MSN argues that the Malate Salt Patents are invalid for lack of written description. (D.I. 169 at 5). Exelixis argues that the Malate Salt Patents have adequate written description. (D.I. 175 at 4).

A. Findings of Fact

1. Crystalline is used as an adjective to describe that the cabozantinib (L)-malate has a “regular repeating underlying arrangement of molecules.” (Tr. 537:22–25).
2. Solid matter can exist as amorphous or crystalline material. (Tr. 846:4–19). Amorphous material is not crystalline. (Tr. 535:16–19, 846:4–19, 853:7–15). A POSA could distinguish between crystalline and amorphous cabozantinib. (Tr. 542:10–25, 846:4–19, 856:6–24, 866:10–867:3).
3. A salt cannot be crystalline without existing in a specific crystalline form (Tr. 440:21–22, 560:13–19).
4. “[A]ll crystalline cabozantinib (L)-malate salts fall within [the] scope” of the asserted claims. (Tr. 558:5–6).

5. The maximum potential size of any pure polymorph genus is fourteen forms. (Tr. 547:2–5).
6. There are three identified species in the genus of crystalline cabozantinib (L)-malate. These are Exelixis' N-1 and N-2 and MSN's form S. (Tr. 455:5:24). There may be up to seven additional identified species in the genus of crystalline cabozantinib (L)-malate salts. These are Mylan's M-2, M-3, and M-4 and Cipla's C-2, C-3, C-4, and C-5. (Tr. 455:5–456:12). There may be one identified primarily-amorphous species of cabozantinib (L)-malate: Mylan's form M-1. (Tr. 865:6–866:1).
7. The specification discloses structural features shared by all crystalline cabozantinib (L)-malate, including chemical name, formula, and structure. ('439 patent at Abstract, 1:26–39, 2:58–3:12, 5:25–6:67; Tr. 866:10–867:3). The specification disclosed two methods of preparation for crystalline cabozantinib (L)-malate, namely, methods of preparing the N-1 and N-2 form. ('439 patent at 18:59–23:60, Tr. 539:10–25).
8. The Malate Salt Patent inventors did not invent any crystalline form of cabozantinib (L)-malate other than Forms N-1 and N-2. (Tr. 902:11–18).
9. The word "form" does not appear in the asserted claims of the Malate Salt Patents. (Tr. 854:22–25).
10. MSN has not proved by clear and convincing evidence that the Malate Salt Patents lack sufficient written description.

B. Legal Conclusions

1. Genus

As an initial matter, the parties dispute whether the Malate Salt Patents claim a genus of crystalline cabozantinib (L)-malate. MSN contends they do. (D.I. 169 at 4–5). Exelixis argues that the Malate Salt Patents do not claim a genus of crystalline cabozantinib (L)-malate. (D.I. 175 at 1). The parties dispute the size of the genus. Exelixis contends the genus consists of three species, whereas MSN argues the genus is eleven species.⁷ (D.I. 169 at 8; D.I. 175 at 4–5).

⁷ I do not determine the size of the genus because, as explained in the analysis, it does not need to be resolved.

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Exelixis presents three arguments for why the claims do not claim a genus of polymorphic forms of crystalline cabozantinib (L)-malate. First, Exelixis argues that “crystalline” is used as an adjective to describe that the cabozantinib (L)-malate has a “regular repeating underlying arrangement of molecules.” (Tr. 537:22–25; D.I. 175 at 10–11). Exelixis does not explain why the use of crystalline as an adjective means the patents do not claim the genus of crystalline cabozantinib (L)-malate. I therefore reject this argument.

Second, Exelixis argues that because the word “form” is not used in the asserted claims, “crystalline” refers to the property of crystallinity, not to specific polymorphic forms. (D.I. 175 at 11). But a salt cannot be crystalline without existing in a specific crystalline form. (Tr. 440:21–22, 560:13–19). The two go hand-in-hand. The claims may not use the word form, but this does not change that using the term “crystalline” means what is claimed is all the “particular polymorph[s]” or “repeating pattern[s]” of the cabozantinib (L)-malate. (Tr. 852:6–7). I therefore reject this argument.

Third, Exelixis argues that because the specification states that N-1 and N-2 are separate disclosures, the Malate Salt Patents do not claim a genus of crystalline polymorphic forms. (D.I. 175 at 11–12, Tr. 851:21–852:16). But what is claimed by a patent reciting “crystalline cabozantinib (L)-malate [i.e., Compound (I)]” if not the genus of crystalline cabozantinib (L)-malate? (Tr. 851:21–852:16). Exelixis does not ask me to limit the claims directed to crystalline cabozantinib (L)-malate to only forms N-1 and N-2. That Exelixis characterizes N-1 and N-2 as separate disclosures does not change that crystalline cabozantinib (L)-malate is the genus.

A genus claim is a “claim[] covering a class of entities characterized by a common property.” Jeffrey A. Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 BERKELEY TECH. L.J. 1141, 1168 (2008). Dr. Steed testified that “all crystalline cabozantinib

(L)-malate salts fall within [the] scope” of the asserted claims. (Tr. 558:5–6). I agree. The claims at issue are genus claims, covering the genus of cabozantinib (L)-malate salts that are characterized by the common property of being crystalline.

2. Analysis

I turn to the question of whether the asserted claims have adequate written description. The parties agree that Exelixis possessed at least two species in the genus of crystalline cabozantinib L malate: N-1 and N-2. (D.I. 169 at 1). N-1 and N-2 are the only forms disclosed in the specification. (Tr. 902:11–18).

Exelixis can satisfy the written description requirement in one of two ways. First, forms N-1 and N-2 could be a “representative number of species falling within the scope of the genus.” *Ariad*, 598 F.3d at 1350. Second, the specification could disclose “structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.” *Id.* (internal citations and quotations omitted). I find that Exelixis satisfies the written description requirement the second way.

I agree with Exelixis that *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725 (Fed. Cir. 2014) [hereinafter *GSK*] is instructive. In *GSK*, the Federal Circuit held that the claims to solvates of dutasteride were adequately described by the patent. *Id.* at 729. The court held, “Describing a complex of dutasteride and solvent molecules is an identification of structural features commonly possessed by members of the genus that distinguish them from others, allowing one of skill in the art to visualize or recognize the identity of the members of the genus.” *Id.* at 730 (cleaned up). The Federal Circuit explained that dutasteride was the key structural component of the solvate complex, and that the description was further narrowed by the requirement that the structure must result from one or any of three processes: reaction,

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precipitation, or crystallization. *Id.* Critical to the Federal Circuit's finding was that "the claim term at issue, 'solvate,' is not functional." *Id.* at 731. The written description for "solvate" thus did not need to meet the more rigorous requirements for written description in support of functional claim language. *Id.*

Here, the claims are directed to crystalline cabozantinib (L)-malate salts. Disclosing the chemical name and formula of cabozantinib (L)-malate, as well as that the structure is crystalline, is "an identification of structural features commonly possessed by members of the genus." *Id.* at 730. The specification also discloses processes used to make the invention. The specification discloses general methods of forming a crystalline salt. ('439 patent at 17:10–18:57). And the specification discloses two methods of preparation for crystalline cabozantinib (L)-malate, namely, methods of preparing the N-1 and N-2 form. ('439 patent at 18:59–23:60, Tr. 539:16–25).

As in *GSK*, the limitation at issue here is structural, not functional. Neither party disputes that crystalline is a structural limitation. Although there are different crystalline polymorphs of cabozantinib (L)-malate, the claims "involve[] no performance property . . . and hence raises no issue of insufficient structural, creation-process, or other descriptions to support such a property." *GSK*, 744 F.3d at 729–30.

Merck is another example in which a court found claims with no functional limitations to be adequately described. *Merck Sharp & Dohme, LLC v. Mylan Pharms. Inc.*, 2022 WL 22855168 (N.D. W.Va. Oct. 26, 2022). "[T]he asserted claims cover[ed] a genus of all forms of the 1-to-1 DHP salt of sitagliptin, including hydrates." *Id.* at *36. At issue was whether Merck possessed the genus of all hydrates of the 1-to-1 DHP salt of sitagliptin, because Merck only possessed and disclosed one species along with its chemical formula and structure. *Id.* However,

the court found there was adequate written description because the “key structural feature of th[e] genus is its unique chemical formula, or structure.” *Id.* The court concluded it “need not address whether Merck also disclosed a representative number of species” since it found adequate written description satisfied by Merck disclosing the key features of the genus. *Id.* at *37.

Here too, the key feature of the genus is the chemical formula and structure of crystalline cabozantinib (L)-malate. All crystalline cabozantinib malate share the same chemical name and formula. (Tr. 558:24–559:3). A POSA would be able to identify whether the structure of a polymorph is crystalline. (Tr. 542:10–25, 846:4–19, 856:6–24, 866:10–867:3). And a POSA could distinguish between crystalline and amorphous cabozantinib. (Tr. 542:10–25, 846:4–19, 856:6–24, 866:10–867:3). This evidence was sufficient for the court in *Merck* to find adequate written description, and I find it is sufficient here.⁸ Since this evidence is sufficient to satisfy written description, I need not determine the size of the genus and whether Exelixis disclosed a representative number of species.

MSN argues that N-1 and N-2 have different crystal structures and physico-chemical properties than the other reported forms. (D.I. 169 at 8). MSN contends that crystalline forms generally have “different densities, melting points, solubilities, hygroscopicity, vapor pressure, and stability.” (*Id.*). MSN argues that the properties of one crystalline form cannot be used to

⁸ The *Merck* court cited expert testimony at trial to explain why the key feature of the genus was the chemical formula or structure. *Merck*, 2022 WL 22855168, at *36. The court cited testimony that “every form of the DHP salt of sitagliptin, whether hydrous or anhydrous, shares the common chemical formula disclosed in the . . . patent.” *Id.* The court further cited expert testimony, “Based on this chemical structure, a POSA using routine techniques would be able to recognize any form of the 1-to-1 DHP salt of sitagliptin and distinguish it from other compounds.” *Id.*

predict the properties of a different form. (*Id.*). MSN contends that the properties of the known crystalline forms of cabozantinib (L)-malate differ. (*Id.*). MSN argues that these differences mean N-1 and N-2 are not representative of the genus, and thus Exelixis cannot meet the written description requirement by disclosing common structural features that are shared by N-1, N-2, and the rest of the genus. (*Id.* at 8–9).

The problem with MSN’s argument is that MSN does not explain why these differences in physico-chemical properties and structure mean N-1 and N-2 are so different from other forms that they are unrepresentative. For example, in *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1291 (Fed. Cir. 2014), the patents in question were directed to human antibodies that help treat psoriasis and rheumatoid arthritis by binding to a particular type of antigen. The Federal Circuit held that the jury heard ample evidence to conclude that the patents were invalid for lack of written description because they “only describe one type of structurally similar anti-bodies and . . . those antibodies are not representative of the full variety or scope of the genus.” *Id.* at 1300. Defendant’s invention fell within the scope of the claimed genus but shared only a “50% sequence similarity” with the claimed antibodies. *Id.* In finding that the claimed antibodies are not representative of the genus, the Federal Circuit cited expert testimony that “antibodies with 80% sequence similarity [to the disclosed antibody] could bind to completely different antigens,” highlighting the “significant structural differences” of the antibodies and “unpredictability of the field of invention.” *Id.* Here, MSN baldly asserts there are differences between N-1, N-2, and the rest of the genus without giving me a framework to evaluate such differences. I reject this argument.

MSN also cites three cases in which the Federal Circuit found inadequate written description for genus claims and argues that the claims here are analogous. (D.I. 169 at 4, 6, 11). I now explain why the three cases are not applicable.

First, MSN cites *ICU Medical, Inc. v. Alaris Medical Systems, Inc.*, 558 F.3d 1368 (Fed. Cir. 2009). In *ICU*, the asserted claims were directed to “medical valves used in the transmission of fluids to or from a medical patient.” *Id.* at 1372. The Federal Circuit held that because the specification described only medical valves with spikes, a POSA would not understand the inventor to have invented a “spikeless” medical valve. *Id.* at 1378. MSN argues that there is inadequate written description because a POSA would not know from the specification “what other forms of crystalline cabozantinib (L)-malate existed, how to make those forms, what the crystal structure of such other forms might be, or what properties each unknown form would have.” (D.I. 169 at 7).

As I have discussed above with regard to the *GSK* and *Merck* cases, I do not think that what MSN alleges a POSA would not know from the specification establishes lack of written description. Furthermore, *ICU* is inapposite because in that case the spike limitation was functional. *ICU*, 558 F.3d at 1375–76. The district court construed it in relevant part as “having a pointed tip for piercing the seal,” and the Federal Circuit affirmed this construction. *Id.* at 1376. Functional claim limitations require more disclosure to meet the written description requirement.⁹ That is not the case here, because there are no functional limitations. A POSA

⁹ See, e.g., *AbbVie*, 759 F.3d at 1301 (“Functionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus.”).

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would understand the inventor to have invented all malate salts of cabozantinib that are crystalline and have the disclosed chemical name and formula.

Second, MSN cites *In re Entresto (Sacubitril/Valsartan) Patent Litigation*, 2023 WL 4405464 (D. Del. July 7, 2023), *appeal docketed*, No. 23-2218 (Fed. Cir.) (scheduled for oral argument on November 13, 2024). The asserted claims covered “valsartan and sacubitril as a physical combination and as a complex.” *Id.* at *17. Because complexes were unknown to a POSA as of the priority date, I found that the inventors could not have possessed complexes of valsartan and sacubitril and held the claims invalid for lack of written description. *Id.* at *22. MSN analogizes to *Entresto* to argue that here, the POSA could not have predicted that there were other forms of cabozantinib (L)-malate in the genus, nor could a POSA predict what polymorph would be obtained before testing. (D.I. 169 at 9–11).

Entresto is distinguishable. I do not think *Entresto* stands for the proposition that a POSA must be able to predict every species in the genus, as MSN argues. In *Entresto*, a POSA would not have known that complexes existed. Here, a POSA would know polymorphic forms of crystalline cabozantinib (L)-malate existed—because Exelixis disclosed two such forms, N-1 and N-2, in the specification. ('439 patent at 18:59–23:60). A POSA must be able to “visualize or recognize the identity of the members of the genus.” *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). A POSA would recognize members of the genus by their chemical name and crystalline structure, features that are common to all species in the genus.

Third, MSN cites *Allergan USA, Inc. v. MSN Laboratories Private Limited*, 694 F. Supp. 3d 511 (D. Del. 2023). That case is no longer good law; after the briefing in this case, it was

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reversed by the Federal Circuit. *Allergan USA, Inc. v. MSN Lab's Priv. Ltd.*, 111 F.4th 1358 (Fed. Cir. 2024). I therefore do not address MSN's arguments based on *Allergan*.

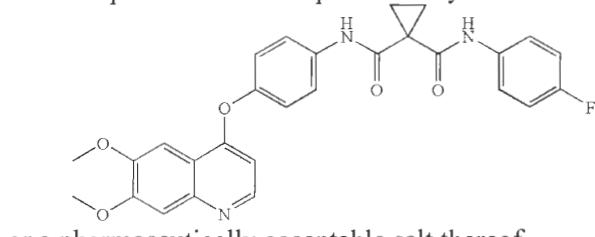
For the reasons stated above, MSN has not met its burden to show by clear and convincing evidence that Exelixis has not adequately described the asserted claims. The asserted claims of the Malate Salt Patents are not invalid for lack of written description.

VI. OBVIOUSNESS-TYPE DOUBLE PATENTING

A. Findings of Fact

1. U.S. Patent No. 7,579,473 (“the ‘473 patent”) issued on August 25, 2009, and is assigned to Exelixis. (DTX-013; Tr. 468:6–11). It expires in 2026. (Tr. 468:23–24).
2. Claim 5 of the ‘473 patent is:

The compound which is represented by the following structure:



or a pharmaceutically acceptable salt thereof.

3. Crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (Tr. 469:24–470:1, 831:9–12, 926:21–927:9).
4. Half of all drug products have APIs in salt form. (Tr. 432:25–433:2). The prior art taught salt formation was a way to improve properties of the API. (Tr. 432:2–433:2). A POSA would want to pursue a salt of cabozantinib (L)-malate to improve its solubility. (Tr. 501:4–6).
5. A POSA would be motivated to form a crystalline salt. (Tr. 441:15–23). A POSA would be motivated to form a salt of cabozantinib.
6. By 2009, salt screening was a known technique used to identify potential salt forms of a drug substance. (Tr. 827:11–16).
7. The pKa of a compound is an inherent property of the compound. (Tr. 436:20–21). It indicates how strong its propensity is to form a salt. (Tr. 436:15–21).

8. A POSA would determine the pKa of the cabozantinib base. It would take a couple weeks to determine the pKa of a base. (Tr. 838:2–24).
9. A POSA would use the decision tree outlined in the Bighley reference to conduct the salt screen. (Tr. 813:7–814:16). A POSA would start by testing hydrochloric acid, then turn to inorganic acids, and then turn to strong organic acids. (Tr. 814:3–817:13). A POSA would not try organic acids unless the inorganic acids did not form an acceptable salt. (Tr. 816:18–817:3).
10. A POSA would use Tong's Rule of 2 to narrow the list of counterions. Tong teaches that to form a salt, the "pKa of the acid should be at least 2 pH units lower than the pKa of the compound," which ensures that the counterion is strong enough to transfer a hydrogen ion to the base, resulting in the formation of a salt. (DTX-243; Tr. 437:3–12). Dr. Trout agreed this "Rule of 2" was a "well-known rule of thumb." (Tr. 931:20–25). Pharmorphix, a company that conducted a salt screen for Exelixis, reported that Pharmorphix used the Rule of 2. (Tr. 622:2–624:21).
11. A POSA would not be motivated to use malic acid as a counterion. (FOF ¶¶ 9–10).
12. A POSA would not have a reasonable expectation of success in forming a crystalline salt of cabozantinib (L)-malate. There is no way of predicting whether a crystalline salt will form. (Tr. 884:1–19).
13. It was unexpected that crystalline cabozantinib (L)-malate displayed the best properties out of all the salts Exelixis evaluated. (Tr. 889:1–10).
14. It was unexpected that crystalline cabozantinib (L)-malate dissolved faster than amorphous cabozantinib (L)-malate. (Tr. 889:11–16, 891:1–9; PTX-225 at 5–8 of 9).
15. It was unexpected that crystalline cabozantinib (L)-malate displayed a fast dissolution profile given its low water solubility. (Tr. 891:1–19).

B. Legal Conclusions

MSN argues that Claim 4 of the '439 patent is invalid for obviousness-type double patenting of Claim 5 of the '473 patent. (D.I. 169 at 12). Claim 5 of the '473 patent covers the cabozantinib compound and "pharmaceutically acceptable salts thereof." ('473 patent at 412:24–51). Claim 4 of the '439 patent covers the crystalline cabozantinib (L)-malate salt. ('439 patent at 32:33–36).

1. Step One

The first step of the obviousness-type double patenting analysis is to construe the asserted claims of the earlier and later-issued patents and determine whether there are differences. *Eli Lilly & Co. v. Barr Lab'ys, Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001).

Here, the issue to be resolved at step one is whether a POSA would have recognized that crystalline cabozantinib (L)-malate is a pharmaceutically acceptable salt of the cabozantinib compound. MSN argues that a POSA would recognize that crystalline cabozantinib (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (D.I. 169 at 12). MSN cites Dr. Steed, Dr. Koleng, and Dr. Trout's testimony that crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (D.I. 169 at 15–16, 34–35).

Exelixis contends that neither the specification of the Malate Salt Patents nor the specification of the '473 patent mention malic acid. (D.I. 175 at 21–22). Exelixis argues that a POSA would not know that crystalline cabozantinib (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (D.I. 175 at 22–23).

I think Exelixis' arguments are more appropriate for step two of the obviousness-type double patenting analysis. The issue under step one is whether there are differences between Claim 4 of the '439 patent and Claim 5 of the '473 patent. See *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1378 (Fed. Cir. 2014) (assuming that the difference under step one of the obviousness-type double patenting analysis is that the asserted claim of the later-issued patent is directed to a species of the reference patent's genus claim). Claim 5 of the '473 patent is very broad. It encompasses the genus of all pharmaceutically acceptable salts of cabozantinib. I credit Dr. Steed, Dr. Koleng, and Dr. Trout's testimony that crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (Tr.

469:24–470:1, 831:9–12, 926:21–927:9). Therefore, Claim 4 of the ’439 patent is directed to a species of the ’473 patent’s genus claim: crystalline cabozantinib (L)-malate.

But the obviousness-type double patenting inquiry does not end here. “[O]bviousness is not demonstrated merely by showing that an earlier expiring patent dominates a later expiring patent. . . . It is well-settled that a narrow species can be non-obvious and patent eligible despite a patent on its genus.” *Mathilda*, 764 F.3d at 1379. If the later expiring patent is an “obvious variation” of the earlier expiring patent, it is invalid for obviousness-type double patenting. *Id.*

I now analyze whether crystalline cabozantinib (L)-malate is “merely an obvious variation” of cabozantinib and its pharmaceutically acceptable salts. *Id.*

2. Step Two

a. Motivation to make a salt of cabozantinib

MSN argues that a POSA would be motivated to make a salt of cabozantinib. MSN argues that the ’473 patent claims the salt form of cabozantinib. (D.I. 169 at 14). Dr. Steed testified that half of all drug products have APIs in salt form, and that the prior art taught salt formation was a way to improve properties of the API. (Tr. 432:2–433:2). These properties include solubility and dissolution rate. (*Id.*).

Exelixis disputes that a POSA would be motivated to form a salt. (D.I. 175 at 23–24). Exelixis contends that MSN must show there is some reason for a POSA to develop a salt when the POSA already had the free base. (*Id.* at 24). Exelixis cites to *Merck* for the proposition, “The mere fact that reference claim 17 covers [the sitagliptin free base and] pharmaceutically acceptable salts of sitagliptin would not, in and of itself, have motivated a POSA to abandon the free base form of sitagliptin to go in search of an acid-addition salt of this compound.” *Merck*, 2022 WL 22855168, at *26. Dr. Steed testified that if there were no problems with the free base,

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then a POSA would pursue the free base as a first formulation option. (Tr. 500:24–501:1). But Dr. Steed also testified that here, there was a solubility issue with the free base, which would be reason to pursue a salt. (Tr. 501:4–6).

Exelixis argues that there were no problems with the free base reported in the prior art, so a POSA would have no reason to make a cabozantinib salt. (D.I. 175 at 24–25). Dr. Trout testified that there was no information disclosed in the prior art about reasons to form a salt of cabozantinib. (Tr. 874:20–23). Dr. Trout testified that a POSA would have considered cabozantinib’s permeability as driving its bioavailability, rather than trying to solve the solubility issue to improve bioavailability. (Tr. 877:11–23).

MSN has shown that a POSA would have been motivated to form a salt of cabozantinib. I find persuasive that a POSA would have wanted to form a salt to increase the solubility, dissolution rate, and other properties of the cabozantinib API. (Tr. 432:2–433:2). This is sufficient reason for a POSA to try to formulate a salt of cabozantinib even though the POSA already had the free base. “Our precedent, however, does not require that the motivation be the best option, only that it be a suitable option from which the prior art did not teach away.” *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014). I find a POSA would be motivated to form a salt of cabozantinib. *See Janssen Pharm., Inc. v. Teva Pharm. USA, Inc.*, 97 F.4th 915, 929–30 (Fed. Cir. 2024) (“A motivation may be found explicitly or implicitly in . . . the background knowledge, creativity, and common sense of the person of ordinary skill.” (internal quotations and citation omitted)).

b. Motivation to use malic acid

MSN outlines the path a POSA would have taken to use malic acid to form cabozantinib (L)-malate. (D.I. 169 at 14–17). MSN contends that a POSA would have started the process of

forming a salt of cabozantinib by testing 15–20 counterions in a salt screen. (Tr. 434:15–25, 470:19–23). MSN argues a POSA would be motivated to select malic acid as one counterion to use in the salt screen. (D.I. 169 at 15).

MSN contends that a POSA would have started with a list of counterions from the prior art. (*Id.*). This list includes fifty counterions, including malic acid. (Tr. 435:6–24). MSN argues a POSA would have narrowed the list to nine by using Tong’s Rule of 2¹⁰ and using only counterions that are generally recognized as safe for administration to humans (“GRAS”). (D.I. 169 at 15; Tr. 475:14–476:1, Tr. 837:15–21, Tr. 932:14–933:1). MSN contends that the nine counterions a POSA would test includes malic acid. (D.I. 169 at 16).

Exelixis disputes MSN’s outline of how a POSA would be motivated to use malic acid on several grounds.

Exelixis contends that a POSA would use the Rule of 3, not Tong’s Rule of 2, to select counterions to use in the salt screen. (D.I. 175 at 30–31). MSN presented evidence that a POSA would know of the Rule of 2 as a rule of thumb, and that the Rule of 2 has been used by a company Exelixis hired to conduct its salt screen. (Tr. 622:2–624:21). “[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available.” *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (cleaned up). That the Rule of 3 existed in the prior art does not mean a POSA would not use Tong’s Rule of 2. I find a POSA would use the Rule of 2 as part of choosing a suitable counterion.

¹⁰ Tong’s Rule of 2 is that a counterion selected for salt screening should have a pKa at least two units lower than the base. (Tr. 437:3–9).

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Exelixis argues that a POSA would not consider a counterion's GRAS status. (D.I. 175 at 30–31). Dr. Koleng testified that GRAS is “related to food additives of the pure materials,” and is “really not directly applicable to pharmaceuticals.” (Tr. 818:13–819:5). Dr. Koleng testified that the safety and toxicity of the salt, not just the counterion, is qualified as GRAS, and that the corresponding acids of the most common counterions used in salt screens are not GRAS. (Tr. 818:20–819:5). I find Dr. Koleng’s testimony persuasive. I do not think a POSA would use a potential counterion’s GRAS status to narrow the list of counterions to test in a salt screen. MSN counters, “The Handbook of Pharmaceutical Salts explicitly provides a ‘List of Salt Formers’ with ‘acids and bases regarded as innocuous’ in which GRAS status is given.” (D.I. 177 at 20, PTX-610 at 336 of 376). But the table lists many qualities of the salt formers, including ones that MSN has not argued a POSA would consider. (PTX-610 at 336 of 376). That the table also lists GRAS status does not convince me a POSA would narrow the list of counterions by excluding any counterion that is not GRAS.

MSN argues that, instead of the method Exelixis proposes a POSA would use to conduct the salt screen, a POSA would use the decision tree outlined in the Bighley prior art reference. (Tr. 813:7–814:16). Dr. Koleng testified that Bighley teaches that a skilled artisan would start a salt screen with hydrochloric acid, because it is a strong acid and very common. (Tr. 814:17–25). After hydrochloric acid, a POSA would turn to inorganic acids because they are strong acids, and, after that, to strong organic acids. (Tr. 815:1–817:13). Dr. Koleng listed the five most common organic acids, and malic acid was not among them. (Tr. 818:2–12).

Based on Dr. Koleng’s testimony, I do not think a POSA would be motivated to select malic acid to test during the salt screen. First, I am persuaded that a POSA would not test every acid in the list of acids to try. Dr. Koleng testified that, consistent with the Bighley reference, a

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POSA would follow a hierarchical approach to pick a salt “in an efficient and timely manner with few false starts and the minimum expenditure of resources.” (Tr. 814:3–16). Dr. Koleng also testified that a POSA would not try organic acids unless the inorganic acids did not form an acceptable salt. (Tr. 816:18–817:3). I find persuasive that, to save resources, a POSA would not try every salt on the list.

Malic acid would be far down on the list of acids a POSA would consider trying. I do not think a POSA would consider GRAS status. Dr. Steed concluded that a POSA, relying on an excerpt of Bighley, would consider organic acids, but I find more persuasive Dr. Koleng’s testimony that the excerpt related to a specific issue for injectable drugs. (Tr. 816:2–17). The drugs at issue here are oral dosage forms, not injectable drugs. (Tr. 816:13–17). Therefore, I do not think a POSA would be motivated to make it far enough down the list of counterions such that the POSA would use malic acid in the salt screen.

MSN argues that a POSA would be motivated to select malic acid because “another FDA-approved tyrosine kinase inhibitor, sunitinib, had been formulated as an (L)-malate salt.” (D.I. 169 at 16 n.3, Tr. 471:8–14). But Dr. Koleng testified that because of sunitinib’s pKa, it would be considered a stronger base than cabozantinib. (Tr. 823:20–824:18). A POSA would be motivated to consider different counterions to use with sunitinib than with cabozantinib. (*Id.*). I find Dr. Koleng’s testimony persuasive, particularly because Exelixis argued that pKa does matter in counterion selection, as per Tong’s Rule of 2. (D.I. 175 at 27–28). I do not think that the formation of sunitinib as an (L)-malate salt would make a POSA consider malic acid in a salt screen of cabozantinib.

MSN contends that Exelixis is improperly arguing about whether malic acid is the best option, not whether it’s a suitable option. (D.I. 177 at 11; *see Par Pharm.*, 773 F.3d at 1197–98).

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I disagree. Because a POSA would follow a hierarchical approach in testing counterions, a POSA would not reach far enough down the list to test malic acid. The question is not whether malic acid is a possible alternative, but whether a POSA would consider it when there were so many more promising alternatives. I find a POSA would not. A POSA would not be motivated to use malic acid to form a salt of cabozantinib.

c. Motivation to form a crystalline salt

Exelixis does not dispute that a POSA would have been motivated to form a crystalline salt. Dr. Steed testified that a crystalline salt is preferred over an amorphous salt because crystalline salts are usually more stable and less hygroscopic. (Tr. 441:15–18). Dr. Steed also testified that prior art shows that drugs in crystalline forms are preferred. (Tr. 441:19–23). I find a POSA would have been motivated to form a crystalline salt.

d. Reasonable expectation of success

MSN argues that a POSA would have a reasonable expectation of forming a crystalline malate salt using a salt screen. (D.I. 169 at 14). Dr. Steed testified that a POSA would expect a solid salt to form after following Tong’s Rule of 2. (Tr. 437:3–438:14).

MSN presents no evidence for whether a POSA would have a reasonable expectation of success of forming a *crystalline* salt. MSN cites Dr. Steed’s testimony that most salts can be crystallized to argue that a POSA would have a reasonable expectation of success of forming a crystalline salt. (D.I. 169 at 16–17). The testimony MSN cites is:

Q. Will a POSA be able to crystallize out of solution all of the pharmaceutical salts that are formed during a salt screen?

A. Not all of them, no. But typically they would be able to isolate a solid, most of them, if only by evaporating off the solvent and then characterize what the result was.

Q. Could you explain what the typical last step of a salt screen is?

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A. Yes. In whatever solids arise from that crystallization attempts, then the person of skill would use routine analytical techniques to characterize the outcome, characterize the residual solids.

Q. And what are the typical properties that will be characterized for each salt that's prepared in a screen?

A. So typically it's crystallinity using x-ray powder diffraction. The sort of properties I alluded to earlier; hygroscopicity, melting point, it's—whether it's a solvate or not, those sorts of things.

Q. And you mentioned one of the properties of a salt is its crystallinity. Can you explain the different—what that is?

A. Yes. So the outcome of the salt screen, if it's a solid it might be either amorphous or crystalline. If it's a crystalline solid, then there will be a regular repeating array of the molecules that give rise to the crystal structure.

(Tr. 438:8–439:16) (cleaned up). I do not think Dr. Steed's testimony that a salt can be crystallized out of solution is the same as the salt being crystalline. Dr. Steed refers to crystallizing a salt out of solution as “isolat[ing] a solid.” (Tr. 438:8–12). Dr. Steed explains that a POSA would characterize the residual solid as crystalline or amorphous. (Tr. 439:9–16). I understand Dr. Steed to be testifying that crystallizing a salt out of solution refers to getting a solid out of solution, which is later characterized as crystalline or amorphous. The testimony was not that a POSA would reasonably expect the solid to be crystalline.

MSN cites Dr. Steed's testimony that a POSA would be motivated to prepare a crystalline form of cabozantinib (L)-malate because more than 90% of pharmaceuticals are in crystalline form. (Tr. 478:19–479:1). But this testimony does not establish that 90% of salts formed through a salt screen are crystalline, nor that a POSA would have a reasonable likelihood of success in obtaining a crystalline salt. MSN cites no other testimony regarding the likelihood of forming a crystalline salt. Exelixis cites Dr. Trout's testimony that there is no way of predicting whether a crystalline salt will form. (Tr. 884:10–19). I find MSN did not meet its burden to show by clear and convincing evidence that a POSA would have a reasonable expectation of success in obtaining a crystalline salt from doing a salt screen with cabozantinib and malic acid.

A POSA would not be motivated to use malic acid to form a salt. A POSA would not have a reasonable likelihood of success in obtaining a crystalline salt using malic acid. Therefore, I find the asserted claims of the Malate Salt Patents are non-obvious.

e. Unexpected Results

Exelixis offers evidence of unexpected results for the Malate Salt Patents. (D.I. 175 at 38–39). Exelixis discusses three examples of unexpected results and incorporates by reference the discussion of commercial success and long-felt need from its obviousness argument for the '349 patent.¹¹ (*Id.*, D.I. 175 at 38 n.14).

I have already found that the asserted claims of the Malate Salt Patents are non-obvious. Exelixis does not prove by a preponderance of the evidence that there are secondary considerations of non-obviousness for the Malate Salt Patents. Exelixis has proven by a preponderance of the evidence that there were unexpected results, but that finding is obviated given that there is no nexus between the Malate Salt Patents and the secondary considerations.

See infra VII.B.2.f.v.

Exelixis argues there were three unexpected results. First, Exelixis argues it was unexpected that crystalline cabozantinib (L)-malate displayed the best properties out of all the salts Exelixis evaluated. (D.I. 175 at 38, Tr. 889:1–10). Second, Exelixis argues it was unexpected crystalline cabozantinib (L)-malate dissolved faster than amorphous cabozantinib (L)-malate. (D.I. 175 at 38–39; Tr. 889:11–16, 891:1–9; PTX-225 at 5–8 of 9). Third, Exelixis

¹¹ I likewise incorporate by reference my later discussion of commercial success and long-felt need. *See infra* VII.B.2.f.i, iii–v. For the reasons set forth there, I find that Exelixis has not proven by a preponderance of the evidence that Cabometyx met a long-felt but unmet need. Exelixis has proven by preponderance of the evidence that Cabometyx was a commercial success but failed to prove a nexus between commercial success, or any other secondary consideration, and the Malate Salt Patents.

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argues it was unexpected that crystalline cabozantinib (L)-malate displayed a fast dissolution profile given its low water solubility. (D.I. 175 at 39, Tr. 891:1–19).

MSN argues that the results argued by Exelixis are not unexpected results, because for a result to be unexpected, it must be unexpected compared to the reference patent. “[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” *In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991). MSN contends that the reference patent is the ’473 patent, and crystalline cabozantinib (L)-malate is within the scope of the patent. (D.I. 177 at 22). Therefore, MSN argues that any property of crystalline cabozantinib (L)-malate is a “latent property” within the scope of the reference claim, rather than an unexpected result. *See In re Pasteur*, 2023 WL 8609987, at *4 (Fed. Cir. Dec. 13, 2023) (“[T]he fact that performing [the] prior art method would produce a result . . . is . . . mere recognition of a latent property in an obvious method of treating pain with the same peptide.” (internal quotations and citation omitted)).

AbbVie sheds light on how to consider unexpected results in the context of an obviousness-type double patenting analysis. The Federal Circuit held, “To determine whether the [asserted] patent is directed to a species that yielded unexpected results, we must necessarily look to the [reference] patent’s disclosures to assess what results were expected at the time the [reference] patent application was filed.” *AbbVie*, 764 F.3d at 1380. Because the study the plaintiff used to show unexpected results in the asserted patent was the same study the reference patent relied on to show utility, the Federal Circuit held that there were no unexpected results. *Id.*

AbbVie teaches that it is not the case that any result of the species claim is a latent property of the reference genus claim. Rather, the reference claim must teach the alleged unexpected result for it to be a latent property. Nothing in the specification of the ’473 patent

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teaches that crystalline cabozantinib (L)-malate displays the best properties, that crystalline cabozantinib (L)-malate dissolves faster than its amorphous counterpart, or that crystalline cabozantinib (L)-malate displays a relatively fast dissolution profile. I reject MSN's argument that there can be no unexpected results of crystalline cabozantinib (L)-malate.

MSN contends that any result cannot be unexpected, because a POSA would not have any "expectation of what the 'suite of properties' for any salt will be before it is formed." (D.I. 177 at 22). MSN cites Dr. Koleng's testimony that there is no way to guarantee a salt would form in a salt screen or what the properties of the salt would be. (Tr. 828:3–12). MSN also cites Dr. Trout's testimony that there is no way to predict the pharmaceutical properties of a salt before it is made and characterized. (Tr. 889:1–6). I do not take this testimony to mean that a POSA would have no expectation of what properties cabozantinib (L)-malate would have. Dr. Trout went on to testify that it was unexpected cabozantinib (L)-malate had the best suite of properties given "potential issues with the low acidity, the high molecular weight, the tendency to form pseudodimerism and also the fact that it has two acid groups." (Tr. 889:7–10). I understand the testimony to reflect that the exact pharmaceutical properties, and thus the efficacy, of a salt cannot be predicted, but that a POSA can have expectations of pharmaceutical properties and efficacy based on other properties of the salt.

MSN argues that the crystalline cabozantinib (L)-malate does not dissolve unexpectedly fast, but that it is the amorphous cabozantinib (L)-malate that dissolves unexpectedly slowly. (D.I. 169 at 35). Dr. Trout testified that not only is it surprising the crystalline cabozantinib (L)-malate dissolved faster than the amorphous cabozantinib malate, but that the crystalline cabozantinib (L)-malate dissolving fully in fifteen minutes, given its low solubility, was unexpected. (Tr. 891:3–9). Against this backdrop, the testimony MSN cites does not persuade

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me that the crystalline form did not have unexpected results. Dr. Steed testified that the solubility of the amorphous cabozantinib (L)-malate was anomalous, explaining that its slow dissolution was surprising because it is hygroscopic and forms clumps.¹² (Tr. 485:5–19). I find persuasive Dr. Trout’s reasoning that the crystalline form dissolving faster than the amorphous form is surprising given its low solubility. (Tr. 891:3–9). There is no reason both results cannot be surprising. It can be unexpected that the crystalline form dissolves more quickly than the amorphous form while also being surprising that the amorphous form dissolves more slowly than expected. Therefore, the Exelixis study showing that amorphous cabozantinib (L)-malate dissolves slowly (Tr. 640:18–641:6) does not prevent me from finding that it was unexpected that crystalline cabozantinib (L)-malate dissolves quickly.

Exelixis has shown by a preponderance of the evidence that the crystalline cabozantinib (L)-malate displayed unexpected results. But, Exelixis has not shown a nexus between the unexpected results and the Malate Salt Patents. *See infra* VII.B.2.f.v.

f. Claim 3 of the '440 patent and Claim 2 of the '015 patent

MSN argues that Claim 3 of the '440 patent and Claim 2 of the '015 patent are not patentably distinct from Claim 5 of the '473 patent. (D.I. 169 at 18).

Claim 3 of the '440 patent recites:

3. A pharmaceutical composition comprising the [cabozantinib] malate salt, wherein said salt is the (L)-malate salt or (D)-malate salt, and wherein said salt is crystalline; and a pharmaceutically acceptable excipient.

('440 patent at 32:16–21).

¹² The transcript is confusing. In one sentence, Dr. Steed says, “So [amorphous cabozantinib (L)-malate] dissolves very quickly.” (Tr. 485:15–16). In the next sentence, Dr. Steed says, “[Amorphous cabozantinib (L)-malate] dissolves unexpectedly slowly.” (*Id.* 485:18). I understand Dr. Steed to be saying that, given its properties, he would expect amorphous cabozantinib (L)-malate to dissolve quickly and it is surprising that it in fact dissolves slowly.

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MSN contends that the only added limitation and difference between Claim 3 of the '440 patent and Claim 5 of the '473 patent is that the '440 patent requires the crystalline cabozantinib (L)-malate to be in "a pharmaceutical composition." (D.I. 169 at 18).

MSN cites Dr. Steed's testimony to argue that it would have been obvious for a POSA make a pharmaceutical composition of cabozantinib. (*Id.*). Dr. Steed testified that the application that led to the '473 patent, U.S. Patent Pub. No. 2007/0054928 (the "'928 application"), "teaches administration of the compounds of the invention or their pharmaceutically acceptable salts which would include the malate salt in appropriate pharmaceutical compositions." (DTX 180; Tr. 481:3–6). Dr. Steed testified that the '928 application does not identify "any specific pharmaceutical compositions with cabozantinib or how to make one." (Tr. 481:7–11). Dr. Steed testified that a POSA would have been able to use the POSA's general knowledge and the prior art to make a pharmaceutical composition of cabozantinib. (Tr. 481:12–20).

I find that MSN has not met its burden of proving by clear and convincing evidence that it would be obvious for a POSA to make a pharmaceutical composition of crystalline cabozantinib (L)-malate. First, MSN has not shown it is obvious for a POSA to make a crystalline cabozantinib (L)-malate salt. But even if MSN had shown it is obvious for a POSA to make crystalline cabozantinib (L)-malate, Dr. Steed's conclusory testimony is not clear and convincing evidence that it would be obvious for a POSA to make a pharmaceutical composition. As MSN argues, Dr. Steed admitted that the '928 application does not disclose "any specific pharmaceutical compositions with cabozantinib or how to make one." (Tr. 481:7–11). Dr. Steed does not explain what a POSA's general knowledge would be that would allow a POSA to turn the salt into a pharmaceutical composition. Dr. Steed does not explain what steps

the POSA would take to create a composition, and whether the steps would be supported by a POSA's general knowledge or prior art. Nor does any other expert.

I turn to evaluating whether Claim 2 of the '015 patent is invalid for obviousness-type double patenting.

Claim 2 of the '015 patent recites:

2. A method of treating cancer, comprising administering to a subject in need thereof [cabozantinib] malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, said salt is crystalline, and said cancer is kidney cancer.

('015 patent at 32:11–16).

MSN contends that the only added limitation and difference between Claim 2 of the '015 patent and Claim 5 of the '473 patent is that the '015 patent requires the additional limitation of administering crystalline cabozantinib (L)-malate as "a method of treating cancer . . . wherein said cancer is kidney cancer." (D.I. 169 at 18).

MSN argues that the '928 application discloses the additional limitation. (*Id.*). Dr. Steed testified that the '928 application discloses treating kidney cancer with cabozantinib and it would be obvious for a POSA to use crystalline cabozantinib (L)-malate to treat kidney cancer. (Tr. 482:9–483:20).

I find that MSN has not met its burden of proving by clear and convincing evidence that it would be obvious for a POSA to treat kidney cancer with the malate salt of cabozantinib. As with the '440 patent, MSN assumes that a POSA could use crystalline cabozantinib (L)-malate as a starting point. However, this assumption fails because MSN has not shown it is obvious for a POSA to make a crystalline cabozantinib (L)-malate salt. Even if I had found MSN had shown a POSA would know how to make crystalline cabozantinib (L)-malate, MSN has not offered clear and convincing evidence that it would be obvious for a POSA to use crystalline cabozantinib (L)-malate to treat kidney cancer. Dr. Steed's testimony, the only testimony MSN cites on this

issue, is highly conclusory. Dr. Steed admitted that the '928 application does not “identify any specific methods or other properties of kidney cancer treatment resulting from administering any of the claimed compounds to a patient.” (Tr. 483:4–9). No expert provided testimony on what method the POSA would use to treat kidney cancer, or how a POSA would go about identifying a successful method.

I find that MSN has not proved by clear and convincing evidence that Claim 3 of the '440 patent and Claim 2 of the '015 patent are invalid for obviousness-type double patenting.

VII. OBVIOUSNESS

A. Findings of Fact

1. Asserted Claim 3 of the '349 patent recites a formulation of cabozantinib (L)-malate that includes a filler, lubricant, disintegrant, and glidant, and is “essentially free” of the 6,7-dimethoxy-quinoline-4-ol impurity (the “1-1 impurity,” *see supra* n.4), where “essentially free” is defined as 200 ppm or less. ('349 patent at 8:15–20, 30:4–51). The '349 patent issued on April 12, 2022, and claims priority to a provisional application filed on February 10, 2011. ('349 patent).
2. There are three routes by which the 1-1 impurity could become present in cabozantinib (L)-malate API—due to the 1-1 impurity being a starting material and carrying through to the final API, due to the formation of the impurity as a degradation product, or due to the formation of the impurity as a byproduct. (Tr. 264:23–265:6, 690:7–13, 657:18–658:1).
3. A POSA would know the 1-1 starting material is potentially genotoxic because it is a quinoline. (Tr. 300:9–21, 304:1–13, 769:3–770:4).
4. A POSA would heed FDA guidance on how to deal with genotoxic impurities. A POSA would be motivated to identify the 1-1 starting material as genotoxic. (Tr. 301:8–10, 302:4–8, 303:5–15).
5. The Brown process, or the A-2 process, is disclosed in Example 1 of Exelixis' 2010 International Patent Application No. WO 2010/083414 to Brown (the “Brown Publication”). (Tr. 606:6–15; DTX-291 at ¶ 0098–00114). It describes how to synthesize cabozantinib (L)-malate API. (Tr. 267:4–268:10). It is a five step process with two side steps. (Tr. 677:11–19, 678:4–13; DTX-291 at ¶ 0098–00114). The A-2 process is an optimized version of an earlier-developed A-1 process. (Tr. 602:4–11).

6. There were four experimental batches prepared of the cabozantinib (L)-malate API. Three were prepared by the contract manufacturer Regis and one was prepared by the contract manufacturer Girindus. (Tr. 603:13–16, 783:7–15).
7. The Regis batches did not follow the Brown experimental process. Regis stated there were some “processing and reagent changes” to the synthetic route they had planned to follow to prepare the batches. (PTX-10 at 9 of 37). Dr. Lepore did not know what those changes were. (Tr. 336:17–338:19).
8. A 1-1 impurity can form as a degradation product during the Brown process. (Tr. 569:16–25, 600:8–601:4, 671:2–20). The so-called “1-3” intermediate material in the A-1 process was found to decompose to form large amounts of the 1-1 impurity. (Tr. 600:19–601:4, 693:3–13, 698:16–18; PTX-35 at 9 of 16). The same decomposition problem occurred in the A-2 process. (Tr. 694:5–12).
9. MSN has not shown by clear and convincing evidence that if the Brown process is followed, it will result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity. (FOF ¶ 8).
10. A POSA would not be motivated to minimize the 1-1 impurity after the Brown process because a POSA would expect that there is, at most, de minimis impurity left at the end of the Brown process. Each step of the Brown process purifies the API. (Tr. 668:16–669:14, 708:23–709:19).
11. Recrystallization of the cabozantinib (L)-malate API is the “first thing” a POSA would have attempted to purify the API if a POSA would have been motivated to minimize the 1-1 impurity after the Brown process. (Tr. 307:23–308:9). Many prior art examples show that recrystallization purifies an API of an impurity. (Tr. 310:11–311:3).
12. A POSA would not be motivated to add a recrystallization step at the end of the Brown process to remove the impurity because a POSA would expect that there is, at most, de minimis impurity left at the end of the Brown process. (Tr. 737:5–15).
13. Recrystallization would not have worked to purify the API of the 1-1 impurity because the impurity would be embedded in the crystalline lattice of the API. (Tr. 735:7–23, 736:13–22). Recrystallization could also produce more 1-1 impurity through “decomposition.” (Tr. 737:5–15).
14. A POSA would not be motivated to obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity. (FOF ¶¶ 11–13).
15. Manufacturing exposes an API to heat, humidity, and excipients, which can cause degradation and thereby lead to increased impurity levels. (Tr. 414:13–24, 689:17–690:6).

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16. A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule that includes a filler, lubricant, disintegrant, and glidant. (Tr. 392:15–394:19).
17. It was not unexpected that cabozantinib (L)-malate could be formulated and stay essentially free of the 1-1 impurity. A POSA would have expected that cabozantinib (L)-malate that is essentially free of the 1-1 impurity could be formulated into a capsule or tablet that is essentially free of the 1-1 impurity. (Tr. 399:18–400:19). The API Exelixis used had very low levels of the 1-1 impurity. (Tr. 612:7–8).
18. The '473 patent is a blocking patent. It issued in 2009. (Tr. 403:17–21). Its published parent application, the '140 publication, would have some discouraging effect similar to that of a weak blocking patent once it was published in August 2005. The '473 patent covered cabozantinib and its pharmaceutically acceptable salts and the '140 publication covered uses of cabozantinib. ('473 patent 411:10–412:57; DTX-192).
19. From August 2005 to the end of the patent term of the '473 patent there would have been some blocking effect. (Tr. 403:9–404:1, 485:23–487:2, 1016:11–14).
20. A POSA would be discouraged from developing technology covered by the '140 publication because the application might be granted and the POSA would then infringe its issued claims. (Tr. 486:20–487:2).
21. There was no successful challenge to the '473 patent or development of others in the 2009 to 2011 time frame. (D.I. 1018:9–11). Competitors would have concerns of losing the invention race to Exelixis and its partners, there was no evidence of a good licensing opportunity due to Exelixis' exclusive collaborations with GSK and BMS, and there was low economic opportunity for others in light of the blocking patent. (Tr. 1018:1–1019:7).
22. In 2019, CIPLA filed an international patent application related to its work investigating cabozantinib. (DTX-121).
23. The purity and stability of the crystalline cabozantinib (L)-malate drives at least part of the commercial success of the drug. (957:22–958:13, 959:4–960:10).
24. There is a nexus between the asserted claims of the '349 patent and the secondary considerations. (FOF ¶ 23; '349 patent at 34:50–51).
25. Cabometyx and Cometriq embody the asserted claims of the '349 patent. (Tr. 422:7–9, 688:12–15).
26. There is no nexus between the Malate Salt Patents and the secondary considerations. (Tr. 894:22–895:2, 1020:13–1022:13).
27. Cabometyx is commercially successful. (Tr. 979:5–6).

28. Cabometyx had \$4.9 billion in sales in four years, and a 39% market share within seven years of its launch. (Tr. 981:14–982:8, 985:8–22). Cabometyx is the market leader for second-line therapy as well as therapies capable of use as a monotherapy or combined therapy. (Tr. 982:20–985:5).
29. Cabozantinib offered only an incremental improvement over existing therapies. (Tr. 996:8–11).
30. Doctors prescribe treatments other than cabozantinib for first-line treatments, and there are other treatments used for second-line treatment. (Tr. 965:22–966:4, 1002:13–20).
31. Cabozantinib does not fulfill the long-felt but unmet need for a safe and effective cancer treatment. (FOF ¶¶ 29–30).

B. Conclusions of Law

At issue is the “essentially free” limitation of Claim 3 of the ’349 patent. MSN argues that Claim 3 of the ’349 patent is invalid because making a cabozantinib (L)-malate API essentially free of the 1-1 impurity would be obvious to a POSA. (D.I. 169 at 20, 26). MSN presents two arguments. First, that the Brown process inherently discloses a cabozantinib (L)-malate API essentially free of the 1-1 impurity. (D.I. 169 at 20). Second, in the alternative, that it would have been obvious for a POSA to modify the Brown process to obtain a formulation of cabozantinib (L)-malate essentially free of the 1-1 impurity. (D.I. 169 at 26).

1. Inherency

MSN argues that the Brown prior art reference inherently discloses a cabozantinib (L)-malate API essentially free of the 1-1 impurity. (D.I. 169 at 20).

In the context of obviousness, proving a claim element is inherent in a prior art reference must meet a high bar. “[T]he concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the natural result of the combination of prior art elements.” *Par Pharm.*, 773 F.3d at 1195 (internal quotations and citation omitted).

Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not

sufficient. . . . If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

In re Oelrich, 666 F.2d 578, 581 (Fed. Cir. 1981).

MSN did not meet its burden of proving inherency by clear and convincing evidence. MSN failed to offer clear and convincing evidence that if the Brown process is followed, it will inherently result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity. The Federal Circuit has found inherency in an obviousness argument when there is both expert testimony of the underlying scientific principles and experimental data showing that the prior art reference inherently discloses the claimed limitation. *See Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1330 (Fed. Cir. 2020); *see also Par Pharm., Inc. v. TWi Pharms., Inc.*, 120 F. Supp. 3d 468, 474 (D. Md.), *aff'd without opinion*, 624 F. App'x 756 (Fed. Cir. 2015). Here, there is neither clear and convincing experimental data nor expert testimony about the underlying scientific principles.

MSN's experimental data does not meet the clear and convincing standard. There were four batches of the cabozantinib (L)-malate API prepared: three by Regis and one by Girindus.¹³ It is undisputed that the three Regis batches all had lower than 100 ppm of the 1-1 impurity and thus met the "essentially free" limitation. (D.I. 169 at 22–23, D.I. 175 at 46). However, I find MSN did not show by clear and convincing evidence that the Regis batches followed the Brown

¹³ There is testimony that the batch produced by Girindus had the highest levels of the 1-1 impurity, ranging as high as 411 or 600 parts per million ("ppm") using HPLC/UV testing. (Tr. 603:5–23, 785:2–10, 789:12–790:3). MSN argues I should disregard the data from the Girindus batch because it does not follow the Brown process. Exelixis argues I should consider the Girindus data and find against inherency. I do not consider evidence of the Girindus batch because even without it, I still find that Brown does not inherently disclose the "essentially free" limitation.

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process. Dr. Lepore testified that the Brown process and Regis process were the same. (Tr. 271:20–275:21, 364:3–365:13). Dr. Lepore walked through the steps of the Brown process and the Regis process and explained that they are virtually identical. (Tr. 271:20–275:21, 364:3–365:13). The document Dr. Lepore relied on for opining on the “synthetic scheme for how Regis went about synthesizing the API, step-by-step reaction by reaction” is a regulatory document Exelixis prepared and submitted to the FDA. (Tr. 271:7–272:3, DTX-38). But in another document Exelixis submitted to the FDA, Regis stated there were some “processing and reagent changes” to the synthetic route it had planned to follow to prepare the batches. (PTX-10 at 9 of 37). Dr. Lepore testified that he had not seen what the changes were, and that he had to assume Exelixis put all the information required of it into its FDA document. (Tr. 336:17–338:19). Dr. Lepore testified, “I'm assuming that these [changes] are extremely minor things that I wouldn't even call deviation.” (Tr. 338:1–3). Because Dr. Lepore did not know what changes Regis made to the Brown process, I do not find persuasive his testimony that the Brown process and Regis process are virtually identical. I cannot find that the Brown process inherently produces a cabozantinib (L)-malate API essentially free of the 1-1 impurity because it is not clear to me that the Regis process followed the Brown process.

MSN's expert testimony about how the underlying science of the Brown process leads to an API essentially free of the 1-1 impurity does not meet the clear and convincing evidence standard. The 1-1 impurity could have formed as a degradation product. MSN cites testimony of various experts who explain that a POSA would not have expected the 1-1 impurity to form as a degradation product.¹⁴ However, what a POSA would have expected is not sufficient to show

¹⁴ Dr. Lepore testified that if a POSA followed the Brown process, the Brown process would always produce an API with less than 200 ppm impurity. (Tr. 299:10–18, 366:14–18). Dr. MacMillan testified that a POSA would not expect any 1-1 impurity to be left at the end of

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inherency, given that Exelixis presented evidence that the 1-1 impurity did form as a degradation product during the Brown process. In response, MSN contends, “[T]here is no evidence that Exelixis’ work discovered the 1-1 impurity formed in any meaningful amount (and certainly not more than 200 ppm) when the Brown Example 1 process was followed.” (D.I. 177 at 17 (cleaned up)). But Dr. Myerson testified that “20[%] of the 1-3 [intermediary] was decomposing to 1-1.” (Tr. 693:11–12). And it is MSN’s burden, not Exelixis’, to show that the Brown process does not form the 1-1 impurity through degradation. I am persuaded by Exelixis’ evidence that the 1-1 impurity could have formed as a degradation product during the Brown process. (Tr. 569:16–25, 600:8–601:4, 671:2–20). I do not find that MSN has met its burden of showing by clear and convincing evidence that the Brown process inherently results in a cabozantinib (L)-malate impurity essentially free of the 1-1 impurity.

2. Obviousness

MSN argues that it would have been obvious for a POSA to modify the Brown process to obtain a formulation of cabozantinib (L)-malate essentially free of the 1-1 impurity. (D.I. 169 at 26).

a. Motivation to identify the 1-1 impurity

Dr. Lepore testified that a POSA would have heeded an FDA document providing guidance on how to deal with genotoxic impurities. (Tr. 310:9–302:8). The FDA document advises a POSA to consider the genotoxicity of starting materials. (Tr. 301:8–10). Specifically, it guides the POSA to look at the structure of the starting material to determine if it is toxic. (Tr. 303:5–15). Dr. Lepore testified a POSA would have followed this guidance, used the Ames test

Brown, because each of the five steps of Brown has a purification component and the reagents added through the process could purge the impurity. (Tr. 668:16–669:14, 677:11–25).

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(which is disclosed in the FDA document) to determine that the 1-1 starting material is a quinoline, and known from the prior art that quinolines are often genotoxic. (Tr. 302:5–306:16). Dr. Myerson agreed that a POSA would know that the 1-1 starting material is potentially genotoxic because it is a quinoline. (Tr. 769:5–770:4).

Exelixis argues that a POSA would not be motivated to minimize the 1-1 impurity¹⁵ because a POSA would not know that the 1-1 starting material is genotoxic. (D.I. 175 at 45). No prior art taught that the 1-1 impurity is genotoxic. (Tr. 356:5–8). But Exelixis does not counter MSN's argument that the FDA guidance would ultimately inform a POSA that the 1-1 starting material is genotoxic. I am persuaded that a POSA would know from the FDA guidance that the 1-1 starting material is genotoxic.

b. Motivation to minimize the 1-1 impurity

Dr. Lepore testified that a POSA would know from the FDA guidance that the 1-1 starting material had to be reduced to the extent technically possible due to its genotoxicity. (Tr. 302:9–18, 307:9–19). Thus, MSN argues a POSA would be motivated to minimize the impurity. (D.I. 169 at 26–27).

Exelixis argues that a POSA would not be motivated to minimize the impurity because a skilled artisan would not expect there to be any impurity left in the final product of the Brown process. (*Id.*). Dr. MacMillan testified that a POSA would read Brown and expect there to be very little impurity left after step one, and no impurity at the end of step five, because each step purifies the API. (Tr. 668:16–669:14). Dr. Myerson testified that by the end of step one, 98% of the starting material is used up. (Tr. 708:23–709:19). Dr. Myerson testified that a POSA would

¹⁵ The parties refer to the 1-1 starting material as the genotoxic material that exists at the start of the Brown process. The parties refer to the 1-1 impurity as whatever is left of the starting material at the end of the Brown process. They are the same material.

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expect a de minimis quantity of the 1-1 impurity to be left at the end, and that a POSA would not expect the 1-1 impurity to form as a degradation product. (*Id.*).

In response, MSN cites Dr. Myerson's testimony that a POSA would have understood from the FDA guidelines that the 1-1 impurity was genotoxic and would need to be minimized. (Tr. 771:17–772:3). MSN contends that Dr. Lepore testified that the FDA Guidance applies to known starting materials even when the starting material is purged in the process. (D.I 169 at 28). But that was not Dr. Lepore's testimony. Dr. Lepore testified that the FDA guidance applies to starting materials and that the guidance states impurities often come from starting materials and need to be controlled. (Tr. 264:23–265:6, 302:1–7). The testimony MSN cites does not convince me that a POSA would try to minimize the 1-1 impurity. I credit Dr. Myerson's testimony that the POSA would think there is, at most, a de minimis amount of impurity left after the Brown process. (Tr. 708:23–709:19; *see also* Tr. 668:16–669:14). A POSA would believe the POSA had already controlled the impurity and thus followed the FDA guidance by following the Brown process.

Because a POSA would not expect that the 1-1 impurity would be present by the end of the Brown process, the POSA would not be motivated to control for it. (Tr. 708:23–709:19; 669:12–14).

c. Motivation to add a recrystallization step

MSN argues that a POSA would be motivated to add a recrystallization step to purify the 1-1 impurity. (D.I. 169 at 28–29).

Exelixis makes the same arguments as above—that a POSA would not think to purify the cabozantinib API further because a POSA would not think any 1-1 impurity would be left by the end of the Brown process. (D.I. 175 at 52). Since I have found a POSA is not motivated to

minimize the 1-1 impurity, I apply the same reasoning to find a POSA would have no motivation to add a recrystallization step to the Brown process.

d. Motivation to obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity

Claim 3 of the '349 patent requires a formulation of cabozantinib (L)-malate that includes a filler, lubricant, disintegrant, and glidant, and is "essentially free" of the 1-1 impurity. ('349 patent at 34:30–51). For MSN to prove the claim to be obvious, MSN must prove two additional requirements: (1) that a POSA would be motivated to ensure the final formulation is essentially free of the 1-1 impurity and (2) that a POSA would be motivated to ensure the final formulation meets the "compositional limitation" of including a filler, lubricant, disintegrant, and glidant.

The second point is easily disposed of, as the parties do not dispute that the POSA would have such a motivation. The parties agree that a POSA would be motivated to formulate the cabozantinib (L)-malate API as a capsule or tablet and ensure the final formulation meets the "compositional limitation." (D.I. 169 at 30–31, D.I. 175 at 54–55). Dr. Donovan testified that a POSA would be motivated by the Brown prior art, the Lachman reference, and the '081 publication "to formulate a cabozantinib (L)-malate tablet or capsule composition with the claimed excipients." (Tr. 394:1–19). I find that a POSA would be motivated to ensure the formulation is a tablet or capsule that includes a filler, lubricant, disintegrant, and glidant.

The parties dispute whether a POSA would be motivated to ensure the final formulation is essentially free of the 1-1 impurity. MSN argues that all that is needed to have a formulation of cabozantinib (L)-malate that is free of the 1-1 impurity is an API free of the impurity. (D.I. 177 at 14). I understand MSN to be arguing that MSN does not need to prove motivation to ensure that the formulation is free of the 1-1 impurity, because if the cabozantinib API is free of the 1-1 impurity, then the formulation would necessarily be free of the 1-1 impurity. Dr. Donovan

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testified that a POSA would expect “to be able to formulate cabozantinib (L)-malate into a capsule that was essentially free of the 1-1 impurity.” (Tr. 399:18–400:19). Dr. Donovan explained that the components, namely cabozantinib (L)-malate that is essentially free of the 1-1 impurity and excipients, can simply be premixed and added to a capsule shell. (*Id.*). Dr. Myerson testified that the “key feature” to “reliably manufacture” a tablet or capsule was formulating an API essentially free of the impurity, so that the formulation would be essentially free of the impurity. (Tr. 697:25–698:7).

But I think that MSN has not proved that the API would be free of the impurity. The 1-1 impurity could appear in the API as a degradation product. (Tr. 569:16–25, 600:8–601:4, 671:2–20). A POSA would not know there might be some 1-1 impurity left at the end of the Brown process. Yet, MSN must show a POSA would be motivated to ensure that the formulation is free of the 1-1 impurity.

MSN argues that a POSA would be motivated to control for the 1-1 impurity during formulation due to prior art references that advise a POSA to minimize and be concerned with stability in formulation. But that testimony deals with choosing excipients that would not cause additional impurities to form. (Tr. 385:1–20, 385:21–386:12, 396:10–16). MSN does not explain how a POSA would control the impurity in the API. MSN has not shown that a POSA would be motivated to obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity.

e. Reasonable expectation of formulating a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity

I do not think a POSA would have a reasonable expectation of success that by using recrystallization the POSA would create a formulation essentially free of the 1-1 impurity. I find persuasive Dr. Myerson’s testimony that recrystallization would not have worked to purify the 1-1 impurity because the impurity would be embedded in the crystalline lattice of the API.

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MSN contends that the first thing a POSA would have tried is recrystallization, and that there are many prior art examples that show recrystallization purifies an API. (D.I. 169 at 29). MSN argues that therefore, a POSA would have a reasonable expectation of success in using recrystallization. (*Id.*). MSN cites *Purdue* for the proposition that “because only routine techniques and commonly possessed training would be required, I find that the POSA would have had a reasonable expectation of success.” *Purdue Pharma L.P. v. Accord Healthcare Inc.*, 669 F. Supp. 3d 286, 317 (D. Del. 2023), *appeal docketed*, No. 23-1953 (Fed. Cir. May 30, 2023). *Purdue* does not help MSN’s argument. In *Purdue* there was no debate that a POSA would be successful using known techniques—the issue was whether a POSA would be motivated to use the known techniques. *Id.* Here, I find that the known technique of recrystallization would not be expected to be successful. While recrystallization might work for many APIs, Dr. Myerson’s testimony is specific to cabozantinib and the 1-1 impurity. Dr. Myerson convincingly explains why in this case, a POSA would not have a reasonable expectation of success in using recrystallization.

f. Secondary considerations/objective indicia of non-obviousness

MSN generally argues secondary considerations in connection with the obviousness challenge to the ’349 patent. (D.I. 169 at 31). But it also incorporated by reference its arguments as to commercial success and long-felt but unmet need into its arguments about double patenting of the Malate Salt Patents. (D.I. 169 at 33). Thus, some of what follows addresses not only the ’349 patent but also the Malate Salt Patents.

Exelixis offers evidence of three secondary considerations of non-obviousness: commercial success, long-felt but unmet need, and unexpected results. (D.I. 175 at 57–58).

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A patentee is not required to present evidence of secondary considerations. See *Prometheus Lab'ys, Inc. v. Roxane Lab'ys, Inc.*, 805 F.3d 1092, 1101–02 (Fed. Cir. 2015). There must be enough evidence, however, for a finding that a given secondary consideration exists by a preponderance of the evidence. See *Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, then the probative value of each secondary consideration will be considered in light of the evidence produced. “It is the fact finders’ job to assess the probative value of the evidence presented.” *Id.* at 1056. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007). That burden stays always with the patent challenger. *Id.*

I think, even without analysis of secondary consideration, Claim 3 of the ’349 patent is non-obvious. Since Exelixis has asserted three secondary considerations, I will take them into account. Exelixis has not proven by a preponderance of the evidence that Cabometyx met a long-felt but unmet need, or that there were unexpected results. Exelixis has proven by preponderance of the evidence that Cabometyx was a commercial success and that there is a nexus between Claim 3 of the ’349 patent and the secondary considerations. But, because I find that the ’473 patent was a blocking patent to the ’349 patent, the commercial success of Cabometyx is not a strong indicator of non-obviousness.

i. Long-felt but unmet need

Exelixis argues there is a long-felt, unmet need for a safe and effective kidney cancer treatment. (D.I. 175 at 58; Tr. 955:2–10). The parties’ dispute centers around whether cabozantinib’s improvement in patient outcomes is sufficient to meet the long-felt, unmet need. (D.I. 169 at 33–34, D.I. 175 at 48).

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This court's discussion of long-felt but unmet need in *Pfizer* is instructive. *Pfizer Inc. v. Mylan Pharms. Inc.*, 71 F. Supp. 3d 458 (D. Del. 2014), *aff'd*, 628 F. App'x 764 (Fed. Cir. 2016) (per curiam). In that case, the court found that the renal cancer drug sunitinib malate met a long-felt but unmet need "for treatments for renal cell carcinoma ('RCC') and pancreatic neuroendocrine tumors ('PNET')." *Id.* at 475. Central to the court's finding was evidence "that sunitinib malate provided greatly improved clinical outcomes for RCC patients, and represented a 'huge paradigm shift' for the treatment of PNET." *Id.*

This court has also found long-felt but unmet need when a new drug helps a portion of patients needing treatment. *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 538 (D. Del. 2016) (finding long-felt but unmet need was fulfilled by an epilepsy drug that was "effective at controlling seizures in a segment of the population who had previously gone without relief from other available [antiepileptic drugs]"), *aff'd*, 890 F.3d 1313 (Fed. Cir. 2018).

I do not think that Exelixis has shown by a preponderance of the evidence that cabozantinib fulfilled a long-felt but unmet need. Dr. George testified that cabozantinib improved patient outcomes for a certain population of patients by "[creating] a treatment option for the first time that extended survival . . . for the majority of patients in the subsequent lines of therapy." (Tr. 949:7–15).

Dr. George did not characterize how much greater patient outcomes were on cabozantinib. He testified only that patients demonstrated "increased overall survival, delayed disease progression, and improved the objective response compared with" other drugs. (Tr. 950:13–19). And Dr. George expressed his understanding that any cancer treatment that would extend the lives of cancer patients beyond previously available therapies would meet a long-felt but unmet need. (961:23–962:2). I interpret Dr. George's testimony to be equating "long-felt but

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unmet need” to “improvement.” But they are not the same thing. Dr. George’s testimony is not sufficient for Exelixis to meet its burden of showing long-felt unmet need by a preponderance of the evidence.

MSN argues that cabozantinib offered only an incremental improvement over existing therapies. (Tr. 996:8–11). I find this argument persuasive. I do not think cabozantinib greatly improved clinical outcomes. Dr. Mega testified that there were other drugs that treated renal cell carcinoma on the market when cabozantinib entered the market. (Tr. 996:22–997:1). And Dr. George admitted that he prescribes treatments other than cabozantinib as a front-line treatment for patients with renal cell carcinoma. (Tr. 965:22–966:4). Dr. Mega testified there are options other than cabozantinib for second-line treatment. (Tr. 1002:13–20). The evidence at trial does not establish that cabozantinib “provided greatly improved clinical outcomes,” “represented a ‘huge paradigm shift,’” or treated patients “who had previously gone without relief.” *See Pfizer*, 71 F. Supp. 3d at 475; *UCB*, 201 F. Supp. 3d at 538. Exelixis has not shown by a preponderance of the evidence that cabozantinib fulfilled a long-felt but unmet need.

ii. Unexpected results

Exelixis argues that it was unexpected that cabozantinib (L)-malate could be formulated and stay essentially free of the 1-1 impurity over time. (D.I. 175 at 59). Exelixis cites Dr. Shah, one of the inventors. Dr. Shah testified that the results of the stability testing were “interesting and surprising” because there was less 1-1 impurity formed than expected given that the impurity “was seen to increase in the presence of moisture, heat, and oxygen.” (Tr. 612:1–11).

MSN argues that the only expert testimony offered was that cabozantinib (L)-malate was very stable and that a POSA would not expect the 1-1 impurity to form as a degradation product. (D.I. 169 at 35; D.I. 177 at 22; *see* Tr. 661:9–24, 663:8–11, 722:7–10). However, the testimony

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that MSN cites from Dr. MacMillan and Dr. Myerson was related to the degradation occurring while forming the API, not during the formulation of the capsule or tablet or while on the shelf.

MSN argues, citing Dr. Donovan, that it was not unexpected that the formulation was essentially free of the impurity because a POSA would have expected that cabozantinib (L)-malate that is essentially free of the 1-1 impurity could be formulated into a capsule or tablet that is essentially free of the 1-1 impurity. (Tr. 399:18–400:19). Exelixis cites testimony that Dr. Shah and his colleagues did not see as much 1-1 impurity as expected because they “were starting at the very low levels of 1-1 in the API.” (Tr. 612:7–8). I therefore find that a POSA would expect that the cabozantinib (L)-malate could be formulated and stay essentially free of the 1-1 impurity. Exelixis has not established unexpected results by a preponderance of the evidence.

iii. Commercial success

Exelixis argues that Cabometyx is commercially successful. (D.I. 175 at 58). In the four years ending in 2020, Exelixis generated \$4.9 billion in revenue from the sale of Cabometyx. (Tr. 985:8–22). Cabometyx obtained a 39% market share of the tyrosine kinase inhibitor market. (Tr. 981:14–982:8). It is the market leader for second-line therapy and therapies capable of use as a monotherapy or combined therapy. (Tr. 984:13–985:5).

“When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention.” *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (internal quotation marks and citations omitted).

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MSN does not dispute Exelixis' data. Instead, MSN argues that Exelixis did not provide any sort of benchmark to evaluate whether the numbers it presents means Cabometyx was successful. (D.I. 169 at 34). MSN argues that Dr. Tate did not determine Cabometyx's profitability because Dr. Tate presented revenue rather than profits or return on investment. (D.I. 177 at 22). But Federal Circuit precedent demonstrates that evidence of sales combined with market share is sufficient to evaluate commercial success. *See, e.g., In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012) ("[T]he more probative evidence of commercial success relates to whether the sales represent a substantial quantity in the market.") (cleaned up); *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1361 (Fed. Cir. 1999) ("[S]ales figures coupled with market data provide stronger evidence of commercial success."); *Alcon Rsch., Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1371 (Fed. Cir. 2012) (holding it was not clearly erroneous that a product was an "outstanding commercial success" based on a "70% market share within two years of its launch" and "nearly \$2 billion in sales within ten years").

Cabometyx had a 26% market share in 2020 and a 39% market share in 2023. (Tr. 981:17–982:2). Cabometyx had \$4.9 billion in sales in four years. (Tr. 985:11–22). I find Cabometyx is a commercial success.

iv. Blocking patent

MSN argues that the '473 patent and its published parent application, the '140 publication, blocked anyone other than Exelixis from commercializing and developing cabozantinib. (D.I. 169 at 33). The '473 patent covers cabozantinib and its pharmaceutically acceptable salts and the '140 publication covers uses of cabozantinib. ('473 patent 411:10–412:57; DTX 192).

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“A patent has been called a ‘blocking patent’ where practice of a later invention would infringe the earlier patent.” *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018). “The existence of such a blocking patent may deter non-owners and non-licensees from investing the resources needed to make, develop, and market such a later, ‘blocked’ invention, because of the risk of infringement liability and associated monetary or injunctive remedies.” *Id.* “If the later invention is eventually patented by an owner or licensee of the blocking patent, that potential deterrent effect is relevant to understanding why others had not made, developed, or marketed that ‘blocked’ invention and, hence, to evaluating objective indicia of the obviousness of the later patent.” *Id.* Where “market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.” *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

As the '473 patent covers the cabozantinib and its pharmaceutically acceptable salts, “no one other than [Exelixis] could have practiced the invention of the ['473 patent] without facing liability for patent infringement.” *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 2017 WL 1199767, at *38 (D. Del. Mar. 31, 2017), *aff'd in part, dismissed in part*, 903 F.3d 1310 (Fed. Cir. 2018).

There were strong disincentives that would have deterred others from developing cabozantinib. (Tr. 1018:1–1019:7). There were no successful challenges to the '473 patent; no development of cabozantinib by others in the 2009 to 2011 time frame; there would have been concerns of losing the invention race to Exelixis and its partners; no evidence of a good licensing opportunity with the exclusive collaborations of Exelixis with GSK and BMS; and low economic

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opportunity for others in light of the blocking patent. (*Id.*). I find that the '473 patent and its published parent application deterred others from developing cabozantinib.

Exelixis raises three arguments for why there is no deterrence because of the '473 patent and '140 publication.

Exelixis cites *Bial-Portela & CA. S.A. v. Alkem Lab'ys Ltd.*, 2022 WL 4244989 (D. Del. Sept. 15, 2022) to argue that the blocking patent does not undermine evidence of commercial success. (D.I. 175 at 59). In *Bial-Portela*, the blocking patent did not obviate commercial success because the blocking patent did not cover the feature of the patent that made it successful. *Bial-Portela*, 2022 WL 4244989, at *14. The blocking patent blocked the compound, but what drove commercial success was the once-daily dosing. *Id.* Exelixis argues that here, the blocking patent may cover the cabozantinib salt, but it is the purity and stability of the cabozantinib (L)-malate, not the cabozantinib salt itself, that drove commercial success. (D.I. 175 at 58–59). I agree that the purity and stability of the crystalline cabozantinib (L)-malate drives at least part of the commercial success of the drug. Exelixis presented expert testimony that it is necessary to control the impurity to have a stable product, that it matters to patients to have a non-genotoxic compound, and that doctors had to stop prescribing drugs after they were found to have genotoxic impurities. (957:22–958:13, 959:4–960:10; see *Bial-Portela*, 2022 WL 4244989, at *14 (“[P]hysicians identifying convenient dosing as a key reason they chose [a product protected by a potential blocking patent] over other options” suggested “that the once-daily dosing was a driver of the commercial success of [the product]”)).

Exelixis argues that several generic companies investigated cabozantinib and applied for patents. (D.I. 175 at 58). Exelixis contends that this evidence shows that the '471 patent and '140 publication did not have a deterrent effect. (*Id.*). MSN cites *Galderma Laboratories* in reply for

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the proposition, “The mere fact that generic pharmaceutical companies seek approval to market a generic version of a drug, without more, is not evidence of commercial success that speaks to the non-obviousness of patent claims.” *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013); (D.I. 177 at 21). *Galderma Labs* is inapposite. Exelixis is not offering evidence that generic companies investigated cabozantinib to show cabozantinib was successful, but to show that the generic companies were not deterred by the blocking patent. But the relevant inquiry is whether the ’473 patent caused a deterrent effect, not whether all others were dissuaded from resource investment. MSN has cited evidence that only itself and CIPLA were investigating cabozantinib. (D.I. 169 at 33; DTX-121). That only two groups investigated cabozantinib suggests Exelixis’ competitors experienced disincentives in investing resources into this area. I find that the ’473 patent deterred investment of resources into making, developing, and marketing the claimed invention.

Exelixis contends that there was no blocking patent for the Malate Salt Patents. (D.I. 175 at 38). The priority date of the Malate Salt Patents is January 16, 2009. (Tr. 428:8–10). The date of the ’140 publication is 2005, and the ’473 patent issued in 2009. (Tr. 9–21). I understand Exelixis’ argument to be that the ’140 publication cannot be a “blocking patent.” That is true, since something that is not a patent cannot be a blocking patent. It does not follow, however, that the ’140 publication is irrelevant. Dr. Steed testified that the ’140 publication “would discourage [others] from adopting, of developing the kind of technology that's covered by [the ’140 publication] just in case the application was granted and then they would infringe claims.” (Tr. 486:24–487:2). Though it does not carry the same deterrent force as the ’473 patent, I find that the ’140 publication had some deterrent effect. It would be a factor to consider by a company

deciding whether to invest resources in investigating cabozantinib, since it had the potential to reduce the return on the company's investment.

v. Nexus

"For secondary considerations to have probative value, the decision maker must determine whether there is a nexus between the merits of the claimed invention and the secondary considerations." *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42 (Fed. Cir. 1985). "[T]he patented invention 'need not be solely responsible for the commercial success' of the accused products in order for a nexus to exist." *IOENGINE, LLC v. Paypal Holdings, Inc.*, 607 F. Supp. 3d 464, 508 (D. Del. 2002) (*citing Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991)). "Whether or not there is a nexus between the novel features of the patented product and the commercial success must be evaluated in terms of what is driving sales." *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 393 (D.N.J.), *aff'd*, 603 F. App'x 999 (Fed. Cir. 2015).

(a) The '349 patent

I think the purity and stability of the crystalline cabozantinib (L)-malate drives at least part of the commercial success of the drug. (FOF ¶ 23). Claim 3 of the '349 patent recites that the formulation is "essentially free" of the 1-1 impurity. ('349 patent at 34:30–51). Therefore, for the '349 patent, there is a nexus between the stability of the drug and its commercial success.

Exelixis argues that a nexus is presumed because "Cabometyx and Cometriq both embody the asserted claims and are coextensive with it." (D.I. 175 at 59–60).¹⁶ "[I]f the

¹⁶ Exelixis is unclear if it intends its embodiment argument for Cabometyx and Cometriq to apply to the Malate Salt Patents as well. In any event, I do not think the argument applies. The Malate Salt Patents have no purity requirements. Thus, since Cabometyx and Cometriq must be essentially free of the 1-1 impurity, they are not coextensive with the Malate Salt Patents.

marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed.” *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). Coextensiveness requires that the “patentee demonstrate that the product is essentially the claimed invention.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1374 (Fed. Cir. 2019). Dr. Myerson and Dr. Donovan testified that Cabometyx and Cometriq embody the asserted claims. (Tr. 688:12–15; Tr. 422:7–9).

MSN argues that the asserted claims “are broad enough to cover devices that either do or do not solve the long-felt need,” so “the evidence of non-obviousness fails because it is not commensurate in scope with the claims.” (D.I. 169 at 32, quoting *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010)) (cleaned up). MSN argues that “an equally viable formulation of cabozantinib (L)-malate that is essentially free of the 1-1 impurity could also be formulated without a glidant, which is outside the scope of the asserted claim.” (D.I. 169 at 32). *Therasense* is inapposite. The Federal Circuit in *Therasense* was addressing the issue of whether the claims and the invention were coextensive, and thus whether the claims included a limitation that solved the long-felt need argued by the patent owner, not whether the claims could be designed around. *Therasense*, 593 F.3d at 1336.

MSN has argued that its formulation is outside the scope of the ’349 claim, and I have so found. MSN does not dispute that Cabometyx and Cometriq embody Claim 3 of the ’349 patent. The purity and stability of the crystalline cabozantinib (L)-malate drives part of the commercial success. Therefore, I find that there is a nexus between Claim 3 of the ’349 patent and the secondary considerations.

(b) The Malate Salt Patents

Exelixis argues that there is a “nexus between the claimed inventions of the Crystalline Malate Salt Patents and Cabometyx and Cometriq: crystalline cabozantinib (L)-malate allows the API to be manufactured and developed in a formulation that is stable, safe, and effective for patients.” (D.I. 175 at 38).

I do not think that Exelixis has met its burden to show by the preponderance of the evidence that the crystalline cabozantinib (L)-malate allows the API to be manufactured in a formulation that is stable, safe, and effective for patients. Dr. Trout’s testimony is insufficient, particularly given that Exelixis made the argument in its briefing that impurities could form in the manufacturing process, after the API is formed. (D.I. 175 at 40). Exelixis cannot have it both ways.

Exelixis has not met its burden to show the requisite nexus between the Malate Salt Patents and the secondary considerations.

I have found a POSA would not be motivated to control for the 1-1 impurity, add a recrystallization step, or obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity. A POSA would not have a reasonable likelihood of success in using recrystallization. Therefore, I find Claim 3 of the ’349 patent is non-obvious.

VIII. CONCLUSION

For the foregoing reasons, I find the asserted claim of the ’349 patent not infringed and not invalid. I find the asserted claims of the Malate Salt Patents not invalid.

The parties shall submit a final judgment consistent with this trial opinion within one week.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,)
)
Plaintiff,)
)
v.) C.A. No. 22-228 (RGA)
) (Consolidated)
MSN LABORATORIES PRIVATE)
LIMITED and MSN PHARMACEUTICALS,)
INC.,)
)
Defendants.)
)

FINAL JUDGMENT

WHEREAS this patent infringement action was brought by Exelixis, Inc. (“Exelixis”) alleging, inter alia, that the submission of Abbreviated New Drug Application (“ANDA”) No. 213878 by MSN Laboratories Private Limited and MSN Pharmaceuticals Inc. (collectively, “MSN”) infringed claim 4 of U.S. Patent No. 11,091,439 (the “‘439 patent”), claim 3 of U.S. Patent No. 11,091,440 (the “‘440 patent”), claim 2 of U.S. Patent No. 11,098,015 (the “‘015 patent”), and claim 3 of U.S. Patent No. 11,298,349 (the “‘349 patent”). *See* D.I. 1 (alleging infringement of claims of ‘439, ‘440, and ‘015 patents);¹ *Exelixis, Inc. v. MSN Labs. Pvt. Ltd.*, C.A. No. 22-945, D.I. 1 (D. Del. July 18, 2022) (alleging infringement of claims of ‘349 patent);

WHEREAS C.A. No. 22-228 (D. Del.) and C.A. No. 22-945 (D. Del.) were consolidated (D.I. 38);

WHEREAS MSN stipulated to infringement of claim 4 of the ‘439 patent, claim 3 of the ‘440 patent, and claim 2 of the ‘015 patent, if those claims were not found invalid (D.I. 26, 1-2);

¹ Unless stated otherwise, references to D.I. refer to the docket index number of filings in C.A. No. 22-228 (D. Del.).

WHEREAS this matter came before the Court for a bench trial to resolve the questions of (1) whether claim 4 of the '439 patent, claim 3 of the '440 patent, and claim 2 of the '015 patent are invalid by reason of lacking an adequate written description; (2) whether claim 4 of the '439 patent, claim 3 of the '440 patent, and claim 2 of the '015 patent are invalid by reason of obviousness-type double patenting; (3) whether the submission of MSN's ANDA No. 213878 constituted infringement of claim 3 of the '349 patent; and (4) whether claim 3 of the '349 patent is invalid by reason of obviousness.

WHEREAS the Court held a bench trial in the above-captioned action from October 23 to October 26, 2023; and

WHEREAS the Court issued an opinion setting forth its findings of fact and conclusions of law on October 15, 2023 (D.I. 186).

IT IS HEREBY ORDERED AND ADJUDGED:

1. Final judgment is entered in favor of Exelixis and against MSN on (1) Exelixis' claim of infringement under 35 U.S.C. § 271(e)(2) of claim 4 of the '439 patent, claim 3 of the '440 patent, and claim 2 of the '015 patent; (2) MSN's claim for a declaratory judgment of non-infringement under 35 U.S.C. § 271(e)(2) of claim 4 of the '439 patent, claim 3 of the '440 patent, and claim 2 of the '015 patent.

2. Final judgment is entered in favor of Exelixis and against MSN on MSN's claim for a declaratory judgment of invalidity of claim 4 of the '439 patent, claim 3 of the '440 patent, and claim 2 of the '015 patent.

3. Final judgment is entered in favor of MSN and against Exelixis on (1) Exelixis' claim of infringement under 35 U.S.C. § 271(e)(2) of claim 3 of the '349 patent and (2) MSN's

claim for a declaratory judgment of non-infringement under 35 U.S.C. § 271(e)(2) of claim 3 of the '349 patent.

4. Final judgment is entered in favor of Exelixis and against MSN on MSN's claim for a declaratory judgment of invalidity of claim 3 of the '349 patent.

5. Final judgment is entered in favor of Exelixis and against MSN that the generic cabozantinib product that is the subject of MSN's ANDA No. 213878, if approved by the FDA, would infringe claim 4 of the '439 patent, claim 3 of the '440 patent, and claim 2 of the '015 patent under 35 U.S.C. § 271(a).

6. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) of any final approval by the FDA of MSN's ANDA No. 213878 shall be a date not earlier than the expiration date of the '439 patent, the '440 patent, and the '015 patent (January 15, 2030), including any extensions and/or additional periods of exclusivity to that date.

7. Pursuant to 35 U.S.C. § 271(e)(4)(B), MSN and any person or entity to whom MSN transfers ANDA No. 213878, along with their respective affiliates, subsidiaries, and each of their officers, agents, servants, and employees, and those acting in privity or concert with them, are hereby enjoined from engaging in the commercial manufacture, use, offer for sale, and/or sale in the United States and/or importation into the United States of the generic cabozantinib product that is the subject of MSN's ANDA No. 213878 until the expiration date of the '439 patent, '440 patent, and '015 patent (January 15, 2030), including any extensions and/or additional periods of exclusivity to that date.

8. In the event that a party appeals this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d) and/or Local Rules 54.1 and/or 54.3, including any motion

that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 30 days after the final disposition of any such appeal, and the responding party shall have 30 days after filing and service to respond.

9. In the event that no party appeals this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d) and/or Local Rules 54.1 and/or 54.3, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 30 days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4, and the responding party shall have 30 days after filing and service to respond.

10. Pursuant to entry of this Final Judgment, all other claims and counterclaims shall be dismissed without prejudice pursuant to Fed. R. Civ. P. 41(a)(2).

Dated this 23 day of October, 2024

/s/ Richard G. Andrews
Honorable Richard G. Andrews
United States District Court Judge

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October 22, 2024

The Honorable Richard G. Andrews
United States District Court
for the District of Delaware
844 North King Street
Wilmington, DE 19801

VIA ELECTRONIC FILING

Re: *Exelixis, Inc. v. MSN Laboratories Private Limited, et al.*
C.A. No. 22-228 (RGA) (Consolidated)

Dear Judge Andrews:

Pursuant to the Court's October 15, 2024 Trial Opinion (D.I. 186), enclosed please find a Proposed Final Judgment for the above-captioned case. The parties have conferred and agree on its form and content.

Respectfully,

/s/ Anthony D. Raucci

Anthony D. Raucci (#5948)

cc: All Counsel of Record (via CM/ECF and e-mail)

8290529



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

September 2, 2022

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THIS OFFICE OF:

PATENT NUMBER: 11,298,349

ISSUE DATE: April 12, 2022

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

Rodney Glover
Certifying Officer



JOINT EXHIBIT

JTX-0004

Case No: 122-cv-00228-RGA-JLH

EXEL2_00004437

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Appx73



US011298349B2

(12) **United States Patent**
Wilson et al.

(10) **Patent No.:** US 11,298,349 B2
(45) **Date of Patent:** *Apr. 12, 2022

(54) **PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS**

(71) Applicant: **Exelixis, Inc.**, Alameda, CA (US)

(72) Inventors: **Jo Ann Wilson**, San Francisco, CA (US); **Khalid Shah**, Half Moon Bay, CA (US)

(73) Assignee: **Exelixis, Inc.**, Alameda, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 17/170,275

(22) Filed: Feb. 8, 2021

(65) **Prior Publication Data**

US 2021/0161885 A1 Jun. 3, 2021

Related U.S. Application Data

(60) Continuation of application No. 17/152,394, filed on Jan. 19, 2021, now abandoned, which is a continuation of application No. 16/706,323, filed on Dec. 6, 2019, now abandoned, which is a division of application No. 16/151,653, filed on Oct. 4, 2018, now Pat. No. 10,543,206, which is a division of application No. 15/348,716, filed on Nov. 10, 2016, now Pat. No. 10,123,999, which is a division of application No. 13/984,559, filed as application No. PCT/US2012/024591 on Feb. 10, 2012, now Pat. No. 9,717,720.

(60) Provisional application No. 61/441,520, filed on Feb. 10, 2011, provisional application No. 61/441,527, filed on Feb. 10, 2011.

(51) **Int. Cl.**
A61K 31/47 (2006.01)
C07D 215/233 (2006.01)

(52) **U.S. Cl.**
CPC *A61K 31/47* (2013.01); *C07D 215/233* (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/47; C07D 215/233
See application file for complete search history.

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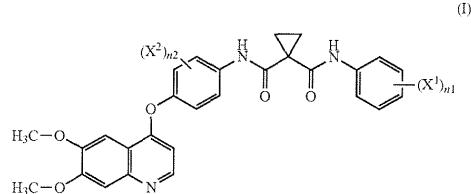
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Primary Examiner — D Margaret M Seaman

(74) *Attorney, Agent, or Firm* — Honigman LLP; Heidi M. Berven

(57) **ABSTRACT**



The present invention is directed to processes for making and compositions containing quinolines such as formula I or pharmaceutically acceptable salts thereof wherein: X1 is H, Br, Cl, or X2 is H, Br, Cl, or n1 is 1-2; and n2 is 1-2.

3 Claims, No Drawings

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1
PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS
CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. Ser. No. 17/152,394 filed Jan. 19, 2021, which is a continuation of U.S. application Ser. No. 16/706,323, filed Dec. 6, 2019, which is a divisional of U.S. application Ser. No. 16/151,653, filed Oct. 4, 2018, now U.S. Pat. No. 10,543,206, which is a division of U.S. application Ser. No. 15/348,716, filed Nov. 10, 2016, now U.S. Pat. No. 10,123,999, which is a divisional of U.S. application Ser. No. 13/984,559, filed Mar. 20, 2014, now U.S. Pat. No. 9,717,720, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty Application No. PCT/US2012/024591, filed Feb. 10, 2012, which claims the benefit of U.S. Provisional Application No. 61/441,520, filed Feb. 10, 2011, and U.S. Provisional Application No. 61/441,527, filed Feb. 10, 2011, the entire contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

This disclosure relates to processes for preparing compounds useful for modulating protein kinase enzymatic activity. More specifically, this disclosure relates to processes for preparing quinolines that are useful for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration, and chemo-invasion and to pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, renal, gastric, head and neck, lung, breast, prostate, and colorectal cancers; hepatocellular carcinoma; as well as in the growth and proliferation of brain tumor cells.

Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., *DN&P* 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Ax1, flt-3, and flt-4.

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The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron, and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation, resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis in vivo (See: Maulik et al *Cytokine & Growth Factor Reviews* 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally, activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., *Cytokine & growth Factor reviews* 2002 13, 41-59; Longati et al., *Curr Drug Targets* 2001, 2, 41-55; Funakoshi et al., *Clinica Chimica Acta* 2003 1-23).

Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A, *Drug Disc. Technol.* 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fins-like tyrosine kinase-4) are both VEGF receptors. Inhibition of EGF, VEGF, and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc. Technol.* 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion with immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human diseases, including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs, and mast cell disease, as well as other disorders associated with activated c-Kit.

Kinase Flt-3 (fins-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly, *Leuk. Lymphoma*, 2003, 44: 1-7).

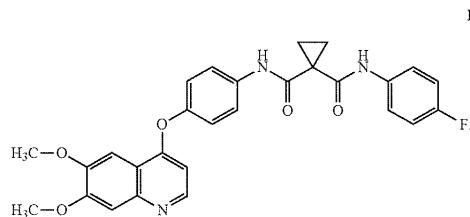
Small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, such as c-Met, VEGFR2, KDR, c-Kit, Ax1, flt-3, and flt-4 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is compound IA, which has the chemical structure:

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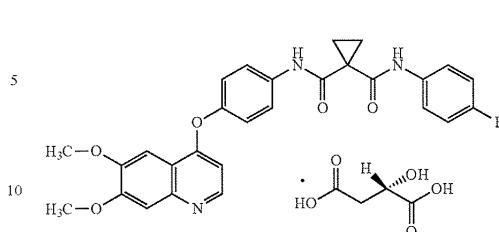
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IA

4



IB

WO2005/030140 describes the synthesis of compound IA (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by reference.

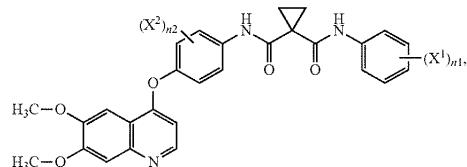
Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug.

Accordingly, there is a need for the discovery of new processes for making quinolines such as compound IA that minimize the formation of undesirable process contaminants or byproducts. There is also a need for new pharmaceutical compositions containing quinolines such as compound IA that are essentially free of process byproducts.

SUMMARY OF THE INVENTION

These and other needs are met by the present disclosure, which is directed to processes for making and compositions containing quinolines or pharmaceutically acceptable salts thereof.

In one aspect, the disclosure relates to processes for preparing a compound of formula I:



I

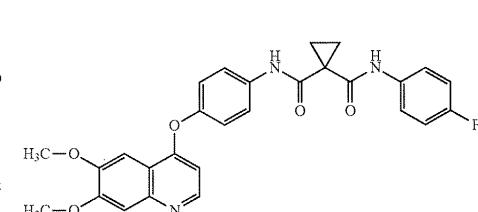
or a pharmaceutically acceptable salt thereof, wherein:
 X^1 is H, Br, Cl, or F;
 X^2 is H, Br, Cl, or F;
n1 is 1-2; and
n2 is 1-2.

Intermediates useful in preparing the above compounds are also disclosed.

The compounds of formula I are useful as protein kinase modulators, and they inhibit various protein kinases including Ret and c-Met.

In another aspect, the disclosure provides a process for preparing compound IB:

from compound IA:

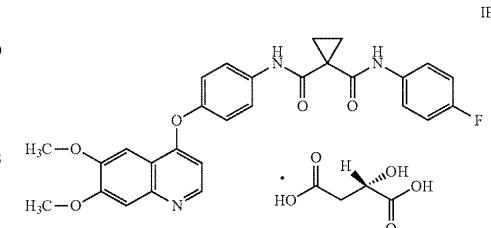


IA

comprising:

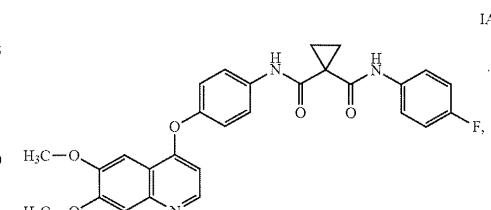
- (a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;
- (b) cooling the mixture;
- (c) vacuum distilling the mixture successively; and
- (d) isolating the compound of IB by filtration.

In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA

comprising:

- (a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

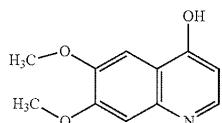
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- (b) cooling the mixture;
- (c) seeding the mixture with compound IB;
- (d) vacuum distilling the mixture; and
- (e) isolating compound IB by filtration.

In another aspect, the disclosure provides compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is



In another aspect, the disclosure provides pharmaceutical compositions containing the compound of formula I, compound IA, or compound IB for oral administration.

In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 1.

TABLE 1

Ingredient	% w/w
Compound I	31.68
Microcrystalline Cellulose (MCC) (Avicel PH102)	38.85
Lactose anhydrous 60M	19.42
Hydroxypropyl Cellulose, EXF	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	95.95
Silicon dioxide, Colloidal	0.30
PWD	
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	100.00

In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2.

TABLE 2

Ingredient	(% w/w)
Compound I	25.0-33.3
Microcrystalline Cellulose, NF	9.8
Hydroxypropyl Cellulose, NF	3
Poloxamer, NF	0-3
Croscarmellose Sodium, NF	6.0
Colloidal Silicon Dioxide, NF	0.5
Magnesium Stearate, NF	0.5-1.0
Total	100

In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2A.

TABLE 2A

Ingredient	% w/w
Compound IB (10% drug load as Compound IA)	12.67
MCC	51.52
Lactose	25.76
Hydroxypropyl cellulose	3.0
Croscarmellose Sodium	6.0

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TABLE 2A-continued

Ingredient	% w/w
Colloidal Silicon Dioxide	0.3
Magnesium Stearate	0.75
Total	100

In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 3.

TABLE 3

Ingredient	mg/unit dose
Compound IB (10% drug load as Compound IA)	25
Silicified Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 4.

TABLE 4

Ingredient	mg/unit dose
Compound IB (50% drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 5, wherein the IB weight equivalents are provided.

TABLE 5

Ingredient	mg/unit dose 50 mg
Compound IB	63.35
Microcrystalline Cellulose	95.39
Croscarmellose sodium	9.05
Sodium starch glycolate	9.05
Fumed Silica	0.54
Stearic acid	3.62
Total Fill Weight	181.00

In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 6, wherein the IB weight equivalents are provided.

TABLE 6

Ingredient	mg/unit dose 60 mg
Compound IB	73.95
Microcrystalline Cellulose	114.36
Croscarmellose sodium	10.85
Sodium starch glycolate	10.85

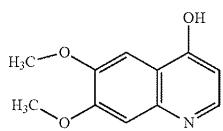
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TABLE 6-continued

Ingredient	mg/unit dose 60 mg
Fumed Silica	0.65
Stearic acid	4.34
Total Fill Weight	217.00

In another aspect, the invention is directed to a pharmaceutical composition comprising compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is



and a pharmaceutically acceptable carrier.

There are many different aspects and embodiments of the disclosure described herein, and each aspect and each embodiment is non-limiting in regard to the scope of the disclosure. The terms "aspects" and "embodiments" are meant to be non-limiting regardless of where the terms "aspect" or "embodiment" appears in this specification. The transitional term "comprising," as used herein, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

The word "can" is used in a non-limiting sense and in contradistinction to the word "must." Thus, for example, in many aspects of the invention a certain element is described as "can" having a specified identity, which is meant to convey that the subject element is permitted to have that identity according to the invention but is not required to have it.

If a group "R" is depicted as "floating" on a ring system, then unless otherwise defined, the substituent(s) "R" can reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

When there are more than one such depicted "floating" groups, such as where there are two groups; then, unless otherwise defined, the "floating" groups can reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

"Pharmaceutically acceptable salts" include acid addition salts.

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"Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or mixtures thereof, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, or mixtures thereof.

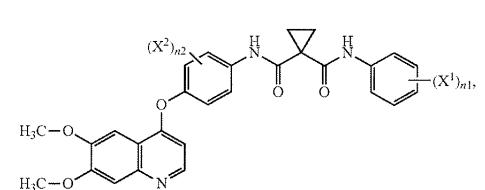
"Essentially free" as used in the phrase "essentially free of process byproducts or contaminants," means that a compound or composition as disclosed here in is admixed with 200 parts per million (ppm) or less of such byproducts or contaminants.

The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them. Unless specified otherwise, the starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic processes.

Processes

Aspect 1: Processes for Making Compounds of Formula I

Aspect (1) of the invention relates to a process of preparing a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X¹ is H, Br, Cl, or F;

X² is H, Br, Cl, or F;

n1 is 1-2; and

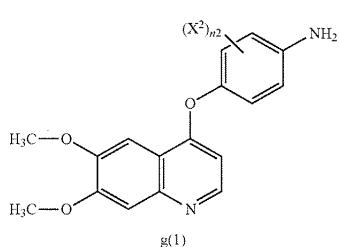
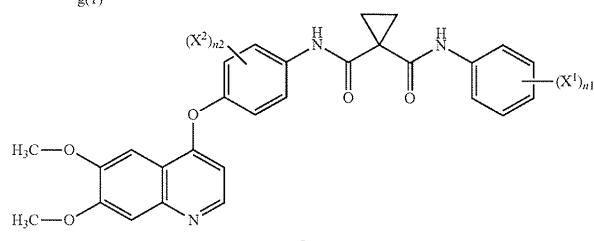
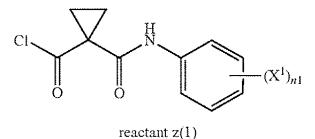
n2 is 1-2;

the process comprising:

contacting the compound of formula g(I) with reactant z(I) to yield the compound of formula I;

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The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using basic conditions. Non-limiting examples of basic conditions that can be used in Aspect (1) include the use of inorganic bases, such as aqueous KOH, NaOH, K₂CO₃, Na₂CO₃, K₃PO₄, Na₃PO₄, K₂HPO₄, Na₂HPO₄, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable solvents. Non-limiting examples of suitable solvents that can be used include water miscible solvents, such as THF, acetone, ethanol, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable temperatures. Suitable temperatures that may be used for the reaction include a temperature at a range from about 10° C. to about 30° C., or alternatively, at a range from about 15° C. to about 28° C., or alternatively, at a range from about 20° C. to about 25° C. The product formed by the reaction is in the free base form, and this free base form may be converted into a pharmaceutically acceptable salt thereof by processes known in the art. For example, the compound of formula I can be converted to the L-malate salt by the addition of L-malic acid and a suitable solvent.

Utilities of the compound of formula I are further described in WO 2005/030140 A2, which is incorporated herein by reference.

Embodiments of Aspect (1) Part A

- In another embodiment of Aspect (1), X¹ is Cl or F.
- In another embodiment of Aspect (1), X² is Cl or F.
- In another embodiment of Aspect (1), X¹ is F.
- In another embodiment of Aspect (1), X² is F.
- In another embodiment of Aspect (1), X¹ is H.
- In another embodiment of Aspect (1), X² is H.
- In another embodiment of Aspect (1), n1 is 1.
- In another embodiment of Aspect (1), n2 is 1.
- In another embodiment of Aspect (1), n1 is 2.
- In another embodiment of Aspect (1), n2 is 2.

All compounds of formula I for Aspect (1) disclosed above include any of the disclosed alternative embodiments

in Part A for each of X¹, X², n1 or n2, in combination with any other of the disclosed alternative embodiments in Part A for each of X¹, X², n1, or n2, as well as a pharmaceutically acceptable salt of any such combination.

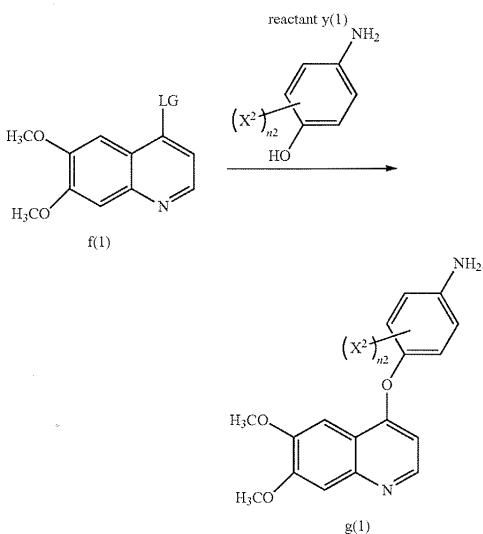
Embodiments of Aspect (1) Part B

- 35 In another embodiment of Aspect (1), n1 and n2 are each 1.
- 36 In another embodiment of Aspect (1), n1 and n2 are each 2.
- 37 In another embodiment of Aspect (1), n1 is 1; and n2 is 2.
- 38 In another embodiment of Aspect (1), n1 is 2 and n2 is 1.
- 39 In another embodiment of Aspect (1), X¹ is H; and X² is F.
- 40 In another embodiment of Aspect (1), X¹ is F; and X² is H.
- 41 In another embodiment of Aspect (1), X¹ and X² are each H.
- 42 In another embodiment of Aspect (1), X¹ and X² are each F.
- 43 In another embodiment of Aspect (1), X¹ is Cl; and X² is H.
- 44 In another embodiment of Aspect (1), X¹ is H; and X² is Cl.
- 45 In another embodiment of Aspect (1), X¹ and X² are each Cl.
- 46 In another embodiment of Aspect (1), X¹ is Cl; and X² is F.
- 47 In another embodiment of Aspect (1), X¹ is F; and X² is Cl.

Embodiments of Aspect (1) Part C

- 65 In an embodiment of Aspect (1), the compound of formula g(1) can be made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of g(1):

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base, such as a metal hydroxide or a non-nucleophilic base. Examples of metal hydroxides include sodium hydroxide or potassium hydroxide. Non-limiting examples of non-nucleophilic bases that can be used include lithium diisopropylamide, lithium tetramethylpiperidine, and alkali metal alkoxides such as sodium tert-butoxide, potassium tert-butoxide, sodium-pentoxide, and the like, or mixtures thereof. Preferably, the base is sodium tert-butoxide or sodium tert-pentoxide. In one embodiment, the base is sodium tert-pentoxide. Typically the sodium tert-pentoxide is commercially available as 35 weight percent solution of base in tetrahydrofuran, or as a 95 weight percent solid reagent. Preferably, the sodium tert-pentoxide is a 95 weight percent solid.

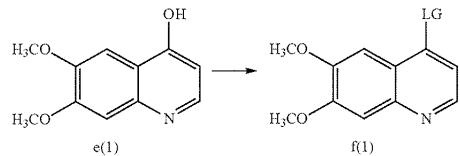
Typically, approximately 1.1 to 3.0 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.3 to 2.5 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.5 to 2.2 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.7 to 2.1 molar equivalents of base are used relative the moles of f(1) that are used.

Typically, the amount of molar equivalents of amino phenol that are used exceeds the molar equivalents of base that are used. In one embodiment, 1.1 to 2 molar equivalents of amino phenol are used relative to the molar equivalents of base that are used.

Once the reaction is substantially complete, the reaction mixture can be cooled to a temperature ranging from about 10° C. to about 25° C. Precooled water can be charged at a rate to maintain a temperature that ranges from about 5° C. to about 35° C. Alternatively, the precooled water can be charged at a rate to maintain a temperature that ranges from about 10° C. to about 25° C. As a non-limiting example, the precooled water can be at a temperature ranging from about 0° C. to about 10° C. As another non-limiting example, the precooled water can be at a temperature ranging from about 2° C. to about 7° C. The precipitate can be collected by filtration under standard conditions and purified by standard purification techniques.

Embodiments of Aspect (1) Part D

In an embodiment of Aspect (1), the compound of formula f(1) can be made by converting a compound of formula e(1) to the compound of formula f(1):



wherein LG represents a leaving group. Non-limiting examples of leaving groups that can be used include halo groups (e.g., Cl, Br, or F) that can be added by halogenating agents. Non-limiting examples of halogenating agents that can be used include chlorinating agents, such as SOCl₂, SO₂Cl₂, COCl₂, PCl₅, POCl₃, and the like.

The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in Part D of Aspect (1) include the use of suitable solvents. Non-limiting example of suitable solvents

wherein LG represents a leaving group, and each of X², and n₂ are as defined in Aspect (1), or as in any of the embodiments of Aspect (1) Part A. A non-limiting example of a leaving group includes a halo group such as Cl, Br, or F. Various compounds of reactant y(1) are commercially available, such as 2-fluoro-4-aminophenol and 4-aminophenol. Also, the skilled artisan would be able to make any variation of reactant y(1) using commercially available starting materials and by using known techniques to modify these commercially available starting materials to yield various compounds within the scope of reactant y(1).

The reaction in this embodiment is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using suitable solvents such as polar solvents. Non-limiting examples of polar solvents that can be used include tetrahydrofuran (THF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), dimethylformamide (DMF), ethyl acetate, N-methyl pyrrolidone (NMP), propylene carbonate, and the like, or mixtures thereof. In another embodiment, the polar solvent is dimethylacetamide (DMA). In another embodiment, the polar solvent is dimethylsulfoxide (DMSO). In another embodiment, the polar solvent is dimethylformamide (DMF). In another embodiment, the polar solvent is ethyl acetate. In another embodiment, the polar solvent is N-methyl pyrrolidone (NMP). In another embodiment, the polar solvent is propylene carbonate. In another embodiment, the solvent is a mixture of solvents, such as a mixture comprising THF and DMA.

The reactants f(1) and y(1) can be added together at a temperature ranging from about 10° C. to about 30° C., or alternatively, from about 15° C. to about 28° C., or alternatively, from about 20° C. to about 25° C. The mixture is then heated to a temperature ranging from about 80° C. to about 125° C., or alternatively, from about 95° C. to about 110° C., or alternatively, from about 100° C. to about 105° C., and the selected temperature is maintained until the reaction is complete.

Other non-limiting examples of suitable reaction conditions in this step of Aspect (1) include the use of a suitable

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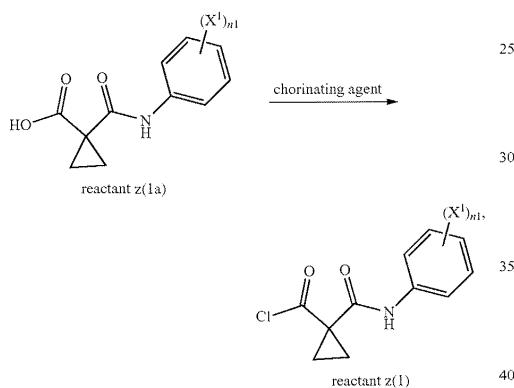
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that can be used during the halogenation of the compound of formula e(1) include a polar, aprotic solvent, such as CH₃CN, DMF, and the like, or mixtures thereof. In other embodiments, the chlorination can be carried out using POCl₃ in acetonitrile, COCl₂ in DMF, or SOCl₂ in DMF. The addition of the chlorination agent is advantageously carried out at a temperature ranging from about 60° C. to about 90° C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 70° C. to about 85° C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 74° C. to about 80° C. The product can then be collected by filtration and purified using standard techniques.

Embodiments of Aspect (1) Part E

In an embodiment of Aspect (1), reactant z(1) can be made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):



wherein X¹ is Br, Cl, or F; and n1 is 1-2. Compounds of reactant z(1a) can be made according to the process described in Example 25 of WO 2005/030140 A2, and the skilled artisan would be able to make any necessary substitutions using commercially available starting materials to come up with various compounds within the scope of reactant z(1a). Example 25 in WO 2005/030140 A2 is incorporated herein by reference.

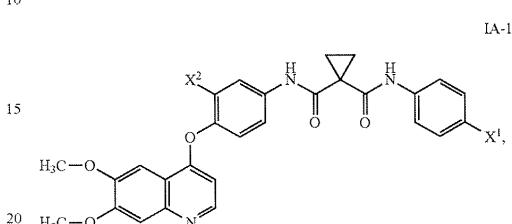
The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using a chlorinating agent such as POCl_3 , oxalyl chloride, and the like. In another embodiment, oxalyl chloride is used as a chlorinating agent. Non-limiting examples of suitable reaction conditions include carrying out the reaction at a temperature in the range from about 0° C. to about 25° C., or alternatively at a temperature in the range from about 5° C. to about 20° C. Other non-limiting examples of suitable reaction conditions include carrying out the reaction in a suitable solvent. Non-limiting examples of suitable solvents that can be used include polar aprotic solvents, such as halogenated hydrocarbons (e.g., dichloromethane and chloroform), ethers (e.g., Et_2O), dioxane, tetrahydrofuran (THF) containing catalytic DMF, and the like, or mixtures thereof. The resulting solution containing

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reactant z(1) can be used, without further processing, to make the compound of formula I.

Other Embodiments of Aspect (1)

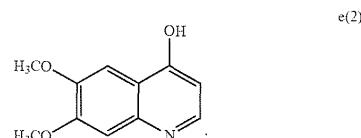
In another embodiment of Aspect (1), the compound of formula I is a compound of formula IA-1:



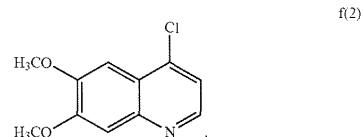
or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Cl, Br, or F; and X^2 is H, Cl, Br, or F. Compound IA can be in the free base form or it can be converted to a pharmaceutically acceptable salt thereof. Accordingly, compound IA can be converted to its L-malate salt by the addition of L-malic acid and a suitable solvent.

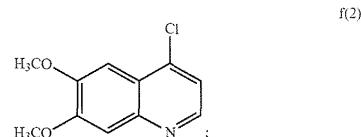
In another embodiment of Part D of Aspect (1), the compound of formula e(1) is compound e(2):



and the compound of formula f(1) is compound f(2);



55 In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):

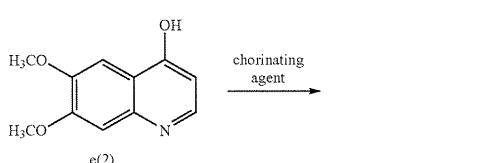


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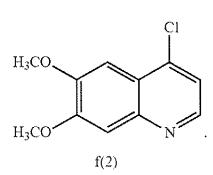
selected from Cl or F. In another embodiment, X¹ and X² for each of formula g(2), and reactant z(1) are both F.

The compound of formula f(2), or a pharmaceutically acceptable salt thereof, can be made by converting the compound of formula e(2) to a compound of formula f(2) with a chlorinating agent in a suitable solvent:



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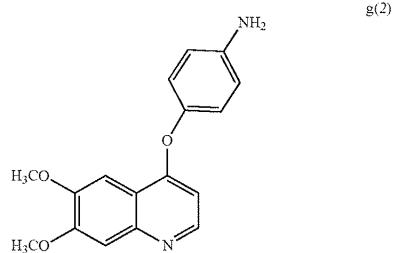
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The compound of formula f(2) can be in its free base form or converted to a pharmaceutically acceptable salt thereof. The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part E of Aspect (1).

Aspect 2: Processes for Making Compounds of Formula g(2)

Aspect (2) of the disclosure relates to a process of preparing compound g(2):



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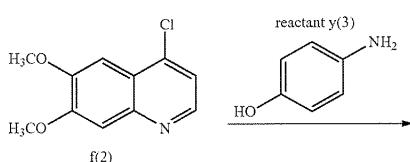
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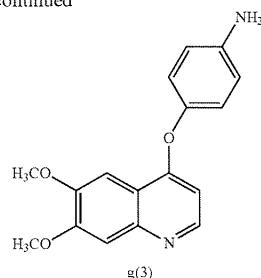
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or a pharmaceutically acceptable salt thereof; the process comprising reacting compound f(2) with reactant y(3) under basic conditions (e.g., using 2,6-lutidine) in an appropriate solvent to yield compound g(3):



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-continued

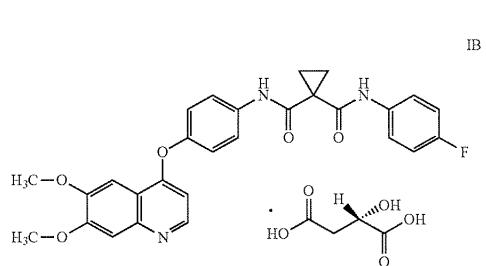


The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part C of Aspect (1).

Alternative reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Parts C and D of Aspect (1).

Aspect 3: Processes for Making Compounds of IB

As indicated above, in one aspect, the invention provides a process for preparing compound IB:



comprising:

- (a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;
- (b) cooling the mixture;
- (c) vacuum distilling the mixture successively; and
- (d) isolating the compound of IB by filtration.

In one embodiment of this aspect, compound IA is admixed with a sufficient amount of L-malic acid in a methylethyl ketone (MEK)/water (1:1) mixture. Alternatively, L-malic acid is added as a solution in water to a mixture of compound IA in methyl ethyl ketone. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70° C., and

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preferably at about 50-60° C., and more preferably at about 55-60° C. with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution. The resulting clear solution is then vacuum distilled from 1 to about 5 times at 150 to 200 mm Hg and a maximum jacket temperature of 55° C. to provide the desired crystalline compound of IB.

In one embodiment, L-malic acid is charged as a solution in water to compound IA. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70° C., and preferably at about 50-60° C., and more preferably at about 55-60° C. with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution which is at a temperature of about 30-40° C., and more preferably at a temperature of about 33-37° C. This clear solution is optionally seeded to facilitate crystallization. After seeding, the resulting mixture is vacuum distilled as provided above.

In one embodiment, compound IB is in the N-1 form. In another embodiment, compound IB is in the N-2 form. In another embodiment, compound IB is a mixture of the N-1 form and the N-2 form. Processes for preparing the N-1 and N-2 forms of compound IB are disclosed in WO 2010/083414 (PCT/US2010021194), the entire contents of which are incorporated herein by reference.

In another embodiment, the disclosure relates to compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the disclosure relates to compound IA admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the disclosure relates to compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the disclosure relates to compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the com-

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ound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

10 In another embodiment, the disclosure relates to compound LB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the disclosure relates to compound IB as a mixture of the N-1 form and the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Pharmaceutical Compositions

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound I, IA, or IB. 40 Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein and are described in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of carriers and excipients used in a composition can be varied proportionally according to the amount of active ingredient used (that is, Compound I, IA or IB).

In one embodiment, the pharmaceutical composition is a tablet.

55 In another embodiment, the pharmaceutical composition is a capsule.

In another embodiment, the pharmaceutical composition comprises Compound IA.

In another embodiment, the pharmaceutical composition comprises Compound IB.

In another embodiment, the pharmaceutical composition comprises Compound IB as the N-1 polymorph.

In another embodiment, the pharmaceutical composition comprises Compound IB as the N-2 polymorph.

65 In another embodiment, the pharmaceutical composition comprises Compound IB as a mixture of the N-1 form and the N-2 form.

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In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants.

In this embodiment, the filler comprises microcrystalline cellulose.

In this embodiment, the disintegrant comprises croscarmellose sodium.

In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

In this embodiment, the glidant comprises fumed silica.

In this embodiment, the lubricant comprises stearic acid.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; lactose; hydroxypropyl cellulose; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; croscarmellose sodium; silicon dioxide; and magnesium stearate.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate.

In another aspect, the disclosure provides a pharmaceutical composition according to Tables 1, 2, 2A, 3, 4, 5, and 6 as provided above. The compositions are prepared according to methods available to the skilled artisan. For example, the Tablet formulations are prepared by combining, blending, and compacting the components of the tablet compositions. The capsule compositions are prepared by combining and blending the components and then placing the blend in a gelatin capsule.

For example, the 25 mg capsules (Table 3, 10 percent drug load formulation) are prepared as follows. The drug substance is delumped through a mill. The delumped drug substance is then co-screened with an equal volume Prosolv HD90. The excipients, except for stearic acid, are screened and charged to a blender along with the co-screened drug substance. The mixture is blended in a V-Blender. This process is repeated to manufacture a second subplot of unlubricated blend. The two subplots are then combined together in a V-blender and lubricated with stearic acid which has been co-screened with an equal volume of unlubricated blend. The final blend is then encapsulated into opaque, size 1 gelatin capsules using an automated capsule filling machine. The capsules are then weight sorted through an automatic weight sorter.

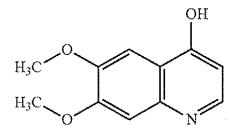
The 100-mg capsules (Table 4, 50% drug load formulation) are manufactured in two equal subplots of 5 kg of blend which are combined prior to lubricant blend. The drug substance is delumped through a mill. The excipients, except for stearic acid, are screened and charged to the mixer along with the delumped drug substance. The mixture is blended with a high shear mixer. The process is repeated to manu-

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facture a second subplot of unlubricated blend. The final blend is then encapsulated into Swedish oraopaque, size 1 gelatin capsules using an automated capsule filling machine. The capsuare then weight sorted through an automatic weight sorter.

The 50 and 60 mg capsules (Tables 5 and 6) are prepared in a similar fashion as the 25 and 100 mg capsules.

In another aspect, the disclosure relates to a pharmaceutical composition comprising a compound of Formula IA or IB and a pharmaceutically acceptable carrier admixed with less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol, 6,7-dimethoxy-quinoline-4-ol, the structure of which is



can be used as reagent e(1) to make chloride f(1) and is a byproduct that may form during the synthesis of Compound IA or IB. Minimizing the concentration of contaminants or byproducts such as 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions destined for human administration is desirable.

In one embodiment, the pharmaceutical composition as defined in any of the previous embodiments (for example, the pharmaceutical composition of Tables 1, 2, 2A, 3, 4, 5, and 6) is admixed with 100 ppm 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 50 ppm 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 25 ppm 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 15 ppm 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 10 ppm 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 5 ppm 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 2.5 ppm 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

In this embodiment, the filler comprises microcrystalline cellulose.

In this embodiment, the disintegrant comprises croscarmellose sodium.

In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

In this embodiment, the glidant comprises fumed silica.

In this embodiment, the lubricant comprises stearic acid.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; admixed with 100 ppm or less of

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6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant croscarmellose sodium; silicon dioxide; and magnesium stearate; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

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25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

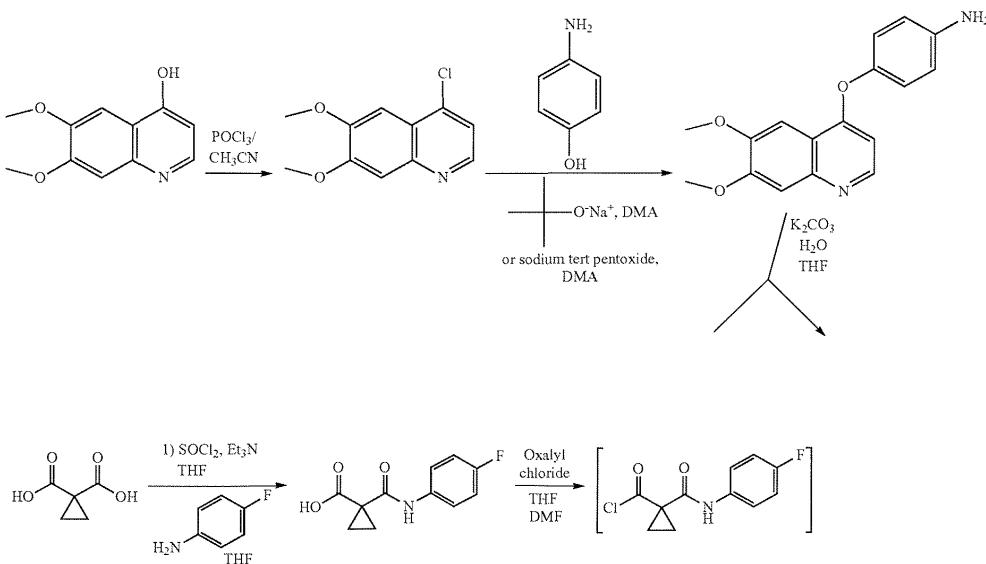
EXAMPLES

The invention is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations. Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon, and the like, will be apparent to those skilled in the art.

Preparation of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof,

A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

Figure 1



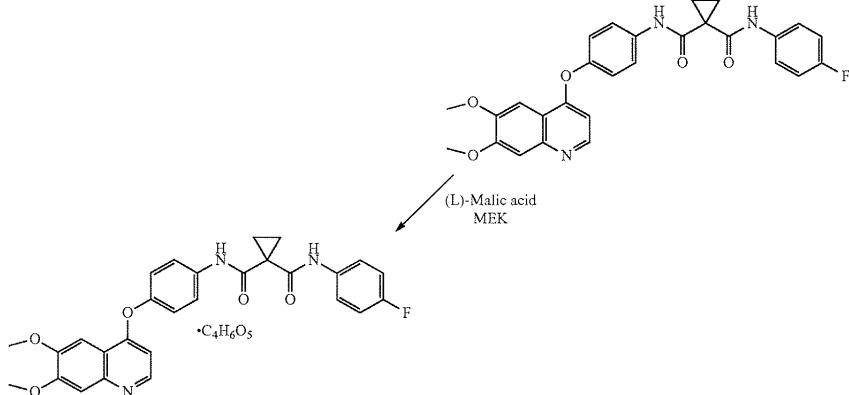
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Preparation of 4-Chloro-6,7-dimethoxy-quinoline

A reactor was charged sequentially with 6,7-dimethoxy-
25 quinoline-4-ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 ° C., and phosphorus oxychloride (POCl_3 , 130.6 kg) was added. After the addition of POCl_3 , the temperature of the reaction mixture was raised to approximately 77 ° C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2-7 ° C. and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26% NH4OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20-25 ° C., and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to -20 to -25 ° C. and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 ° C. under nitrogen to afford the title compound. (35.6 kg).

Preparation of
4(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine

4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20-25 ° C. This mixture was then heated to 100-105 ° C. for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 ° C. and water (pre-cooled, 2 to 7 ° C., 587 L) charged at a rate

to maintain 15 to 30 ° C. temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25 ° C. on filter to yield crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine was refluxed (approximately 75 ° C.) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1 hour and then cooled to 0-5 ° C. and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25 ° C. to yield 4-(6,7-dimethoxy-
35 quinoline-4-yloxy)-phenylamine (34.0 kg).

Alternative Preparation of
4(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine

40 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-amino-
phenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents)
88.7 kg, 35 wt percent in THF) were charged to a reactor,
followed by N,N-dimethylacetamide (DMA, 293.3 kg). This
mixture was then heated to 105-115 ° C. for approximately 9
hours. After the reaction was deemed complete as determined
using in-process HPLC analysis (<2% starting material remaining),
the reactor contents were cooled at 15 to 25 ° C. and water (315 kg)
45 was added over a two hour period while maintaining the temperature between 20 and 30 ° C.
The reaction mixture was then agitated for an additional hour at 20 to 5 ° C. The crude product was collected by
50 filtration and washed with a mixture of 88 kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried
on a filter drier for 53 hours. The LOD showed less than 1%
55 w/w.

In an alternative procedure, 1.6 equivalents of sodium
tert-pentoxide were used and the reaction temperature was
increased from 110-120 ° C. In addition , the cool down
temperature was increased to 35-40 ° C. and the starting
60 temperature of the water addition was adjusted to 35-40 ° C.,
with an allowed exotherm to 45 ° C.

Preparation of 1-(4-fluoro-phenylcarbamoyl)-cyclo-
propanecarboxylic acid

65 Triethylamine (19.5 kg) was added to a cooled (approximately 5 ° C) solution of cyclopropane-1,1-dicarboxylic acid

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(24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5° C. The solution was stirred for approximately 1.3 hours, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10° C. When the addition was complete, the solution was stirred for approximately 4 h keeping temperature below 10° C. A solution of 4-fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10° C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50% dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40° C. followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-heptane (102.4 kg) resulting in wet crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (29.0 kg). The crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25° C. followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25° C. under nitrogen to afford the title compound (25.4 kg).

**Preparation of
1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl
chloride**

Oxalyl chloride (12.6 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25° C. This solution was used in the next step without further processing.

**Alternative Preparation of
1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl
chloride**

A reactor was charged with 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175 kg THF. The reaction mixture was adjusted to 12-17° C. and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12-17° C. for 3 to 8 hours. This solution was used in the next step without further processing.

**Preparation of cyclopropane-1,1-dicarboxylic acid
[4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-
amide (4-fluoro-phenyl)-amide (Compound IA)**

The solution from the previous step containing 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30° C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20-25° C. for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered

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by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25° C. and then at approximately 45° C. under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide

A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 K₂CO₃ in 169 kg water. The acid chloride solution of described in the Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20-30° C. over a minimum of two hours. The reaction mixture was stirred at 20-25° C. for a minimum of three hours. The reaction temperature was then adjusted to 30-25° C. and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25° C. for a minimum of 16 hours.

The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35° C. for approximately 30 minutes. 456 kg water was then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours. The mixture was agitated at 15-25° C. for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 THF in two portions. The product was dried at a maximum temperature set point of 40° C.

In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15° C. The recrystallization temperature was changed from 15-25° C. to 45-50° C. for 1 hour and then cooled to 15-25° C. over 2 hours.

**Preparation of cyclopropane-1,1-dicarboxylic acid
[4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-
amide (4-fluoro-phenyl)-amide, (L) malate salt
(Compound IB)**

Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74° C.) for approximately 2 hours. The reactor temperature was reduced to 50 to 55° C. and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF≤0.5% w/w) at approximately 74° C. The temperature of the reactor contents was reduced to 20 to 25° C. and held for approximately

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4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50° C. to afford the title compound (45.5 kg).

Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt

Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (47.9 kg), L-malic acid (17.2), 658.2 kg methyl ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50-55° C. for approximately 1-3 hours, and then at 55-60° C. for an addition at 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25° C. and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55° C. to the volume range of 558-731 L.

The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide by charging 159.9 kg methyl ethyl ketone to give a total volume of 880L. An addition at vacuum distillation was carried out by adjusting 245.7 methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20-25° C. for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45° C.

In an alternative procedure, the order of addition was changed so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

Preparation of Compound IB, Form N-1

A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{[6,7-bis(methoxy)-quinolin-4-yloxy]phenyl}-N'-4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60° C. and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

At 60° C., acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60° C. for 10 hours. The solution was then cooled to 20° C. and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR; 1.20 L). The solids were dried at 60° C. (25 mm Hg) for 6 hours to afford compound (I), Form N-1 (108 g; 0.85 equivalent; 108.00 g; 85.22% yield) as a white crystalline solid.

Alternate Preparation of Compound IB, Form N-1

A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-{[6,7-bis(methoxy)-

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quinolin-4-yloxy}phenyl)-N'-4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 hours with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

Separately, a powder blend was made with known amounts of two batches of compound IB: (1) 300 mg of batch 1, which contained approximately 41% compound IB, Form N-1 and 59% compound IB, Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to compound IB, Form N-2.

The compound LB, Form N-1 and compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45° C. to afford 128 mg of crystalline compound IB in the N-1 form.

Preparation of Crystalline Compound IB, Form N-2

Preparation of Crystalline Compound IB, Form N-2 Seed Crystals

A solution was prepared by combining 20 ml of acetone and 300 mg of compound IA (N-(4-{[6,7-bis(methoxy)-quinolin-4-yloxy}phenyl)-M-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide) in a 25 ml screw capped vial. Next, 0.758 ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hours at ambient temperature. The sample was then suction filtered with 0.45 μm PTFE filter cartridge and dried in vacuo at ambient temperature overnight.

Preparation of Crystalline Compound IB, Form N-2.

To a reactor were added N-(4-{[6,7-bis(methoxy)-quinolin-4-yloxy}phenyl)-N'-4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50° C. Seed crystals were added (1%, 480 mg) and the malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 mL/min over 3 hours). The slurry was held at 50° C. for 18 hours and then was cooled to 25° C. over 30 minutes. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL). The solids were dried under vacuum at 60° C. for 5 hours to afford compound IB (55.7 g; 0.92 equivalent; 55.70 g; 91.56% yield) as an off-white crystalline solid.

Stability Studies of Pharmaceutical Compositions

The pharmaceutical capsule compositions of Tables 3 and 4 were prepared by mixing the ingredients according to processes known in the art.

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TABLE 3

Ingredient	mg/unit dose
Compound IB (10% drug load as Compound IA)	25
Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

TABLE 4

Ingredient	mg/unit dose
Compound IB (50% drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

The capsule compositions were subjected to stability studies to monitor the formation of 6,7-dimethoxy-quinoline-4-ol at various temperatures and relative humidities over time. The results are summarized in Tables 7A and 7B and Tables 8A and 8B.

TABLE 7A

Stability of 25 Mg Capsules (Table 3)					
	Conditions	Bottle A1	Bottle A2	Bottle A3	Bottle A4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T = 0	25° C./60% RH	2	2	3	3
1 Month	25° C./60% RH	3	4	5	NA
	30° C./75% RH	4	4	NA	NA
	40° C./75% RH	9	9	10	NA
3 Months	25° C./60% RH	5	5	7	NA
	30° C./75% RH	7	6	NA	NA
	40° C./75% RH	22	23	24	NA
6 Months	25° C./60% RH	6	6	7	7 (3 M in blister)
	30° C./75% RH	9	9	NA	NA
	40° C./75% RH	40	44	43	27 (3 M in blister)
9 Months	25° C./60% RH	7	7	9	8 (6 M in blister)
	30° C./75% RH	13	12	NA	NA

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TABLE 7A-continued

5	Conditions	Stability of 25 Mg Capsules (Table 3)			
		Bottle A1	Bottle A2	Bottle A3	Bottle A4
	PPM of 6,7-dimethoxy-quinoline-4-ol				
	RH 40° C./75%	NA	NA	68	60 (6 M in blister)

M = Months;
NA = Not Applicable;
RH = Relative Humidity;
PPM = Parts per Million. A portion of Bottle A4 was repackaged in a blister pack after being stored in bottles for 3 months.

TABLE 7B

20	Conditions	Stability of 25 Mg Capsules (Table 3)			
		Bottle B1	Bottle B2	Bottle B3	Bottle B4
	PPM of 6,7-dimethoxy-quinoline-4-ol				
	25° C./60% RH	3	1	2	2
1 Month	25° C./60% RH	<2	<2	<2	NA
	30° C./75% RH	<2	<2	NA	NA
	40° C./75% RH	2	<2	<2	NA
3 Months	25° C./60% RH	2	<2	<2	NA
	30° C./75% RH	2	<2	NA	NA
	40° C./75% RH	3	<2	<2	NA
6 Months	25° C./60% RH	<2	<2	<2	<2 (3 M in blister)
	30° C./75% RH	2	<2	NA	NA
	40° C./75% RH	4	<2	3	3 (3 M in blister)
9 Months	25° C./60% RH	<2	<2	<2	<2 (6 M in blister)
	30° C./75% RH	3	<2	NA	NA
	40° C./75% RH	NA	NA	5	4 (6 M in blister)

A portion of Bottle B4 was repackaged in a blister pack after being stored in bottles for 3 months.

TABLE 8A

60	Conditions	Stability of 100 Mg Capsules (Table 4)			
		Bottle A1	Blister A2	Bottle A3	PPM of 6,7-dimethoxy-quinoline-4-ol
	Initial T = 0	25° C./60% RH	4	4	6
	1 Month	25° C./60% RH	4	4	6
		30° C./75% RH	4	NA	6
		40° C./75% RH	6	6	9

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TABLE 8A-continued

Conditions	Bottle A1	Blister A2	Bottle A3
	PPM of 6,7-dimethoxy-quinoline-4-ol		
3 Months	25° C./60% RH	5	5
	30° C./75% RH	6	NA
	40° C./75% RH	10	10
6 Months	25° C./60% RH	5	5
	30° C./75% RH	6	NA
	40° C./75% RH	11	17

M = Months;
NA = Not Applicable;
RH = Relative Humidity;
PPM = Parts per Million.

TABLE 8B

Conditions	Bottle B1	Blister B2	Bottle B3
	PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T = 0	25° C./60% RH	1	1
	25° C./60% RH	<2	<2
	30° C./75% RH	<2	<2
3 Months	25° C./60% RH	<2	<2
	30° C./75% RH	<2	NA
	40° C./75% RH	<2	2
6 Months	25° C./60% RH	<2	<2
	30° C./75% RH	<2	NA
	40° C./75% RH	2	2

M = Months;
NA = Not Applicable;
RH = Relative Humidity;
PPM = Parts per Million.

The results summarized in Tables 7A and 7B and 8A and 8B indicate that formation of 6,7-dimethoxy-quinoline-4-ol was minimized to 50 ppm or less over time in the capsule formulations.

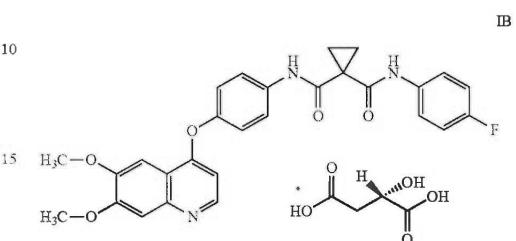
The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following

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appended claims, along with the full scope of equivalents to which such claims are entitled. All references cited herein are incorporated by reference in their entirety.

The invention claimed is:

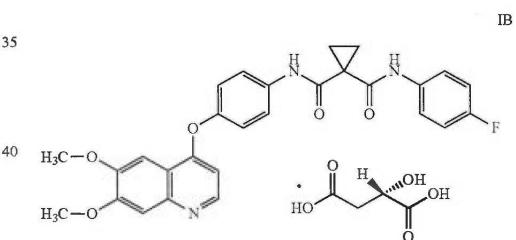
- 5 1. A pharmaceutical composition for oral administration comprising Compound IB;



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

20 2. The pharmaceutical composition of claim 1, wherein the process byproduct or contaminant is 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical composition.

25 3. A pharmaceutical composition for oral administration comprising Compound IB;



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition; and wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.

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PATENT NUMBER: 11,091,439

ISSUE DATE: *August 17, 2021*

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JOINT EXHIBIT

JTX-0001

Case No: 1:22-cv-00228-RGA-JLH

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(12) **United States Patent**
Brown et al.

(10) **Patent No.:** US 11,091,439 B2
(45) **Date of Patent:** *Aug. 17, 2021

(54) **MALATE SALT OF N-(4-[6,7-BIS(METHYLOXY)QUINOLIN-4-YL]OXY)PHENYL)-N'-(4-FLUOROPHENYL)CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEREOF FOR THE TREATMENT OF CANCER**

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CPC *C07D 215/22* (2013.01); *C07D 215/233* (2013.01)

(58) **Field of Classification Search**
CPC *C07D 215/22; C07D 215/233*
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are malate salts of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including a (L)-malate salt, a (D)-malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

5 Claims, 27 Drawing Sheets

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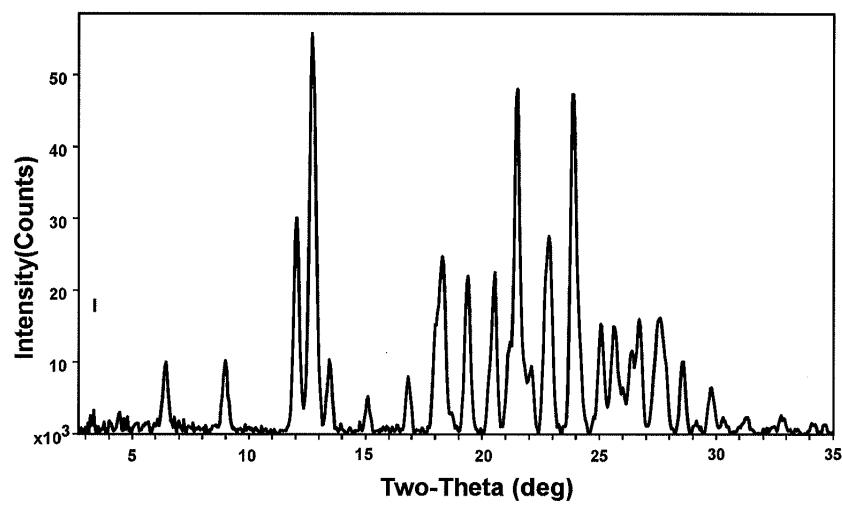
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Figure 1



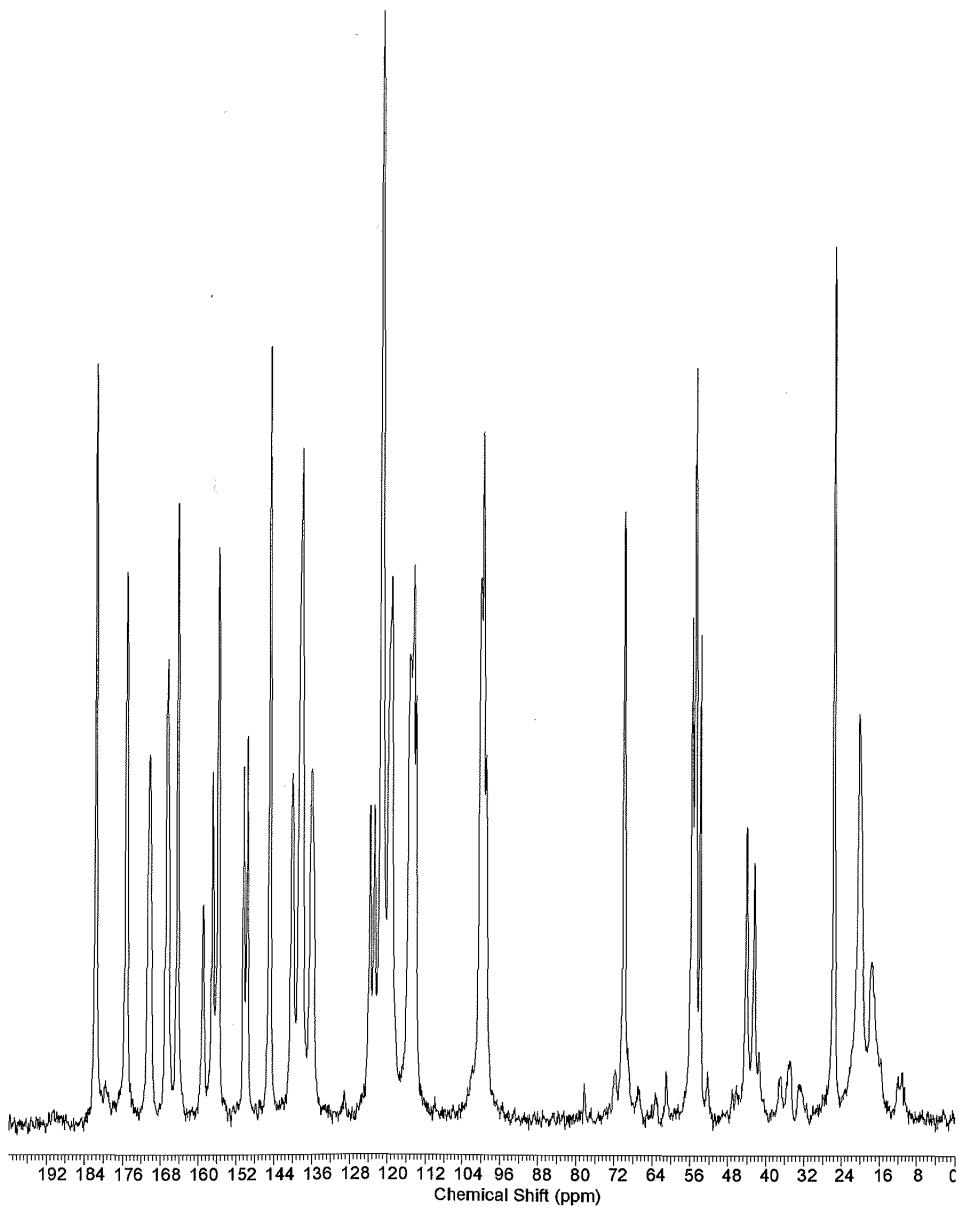
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Figure 2



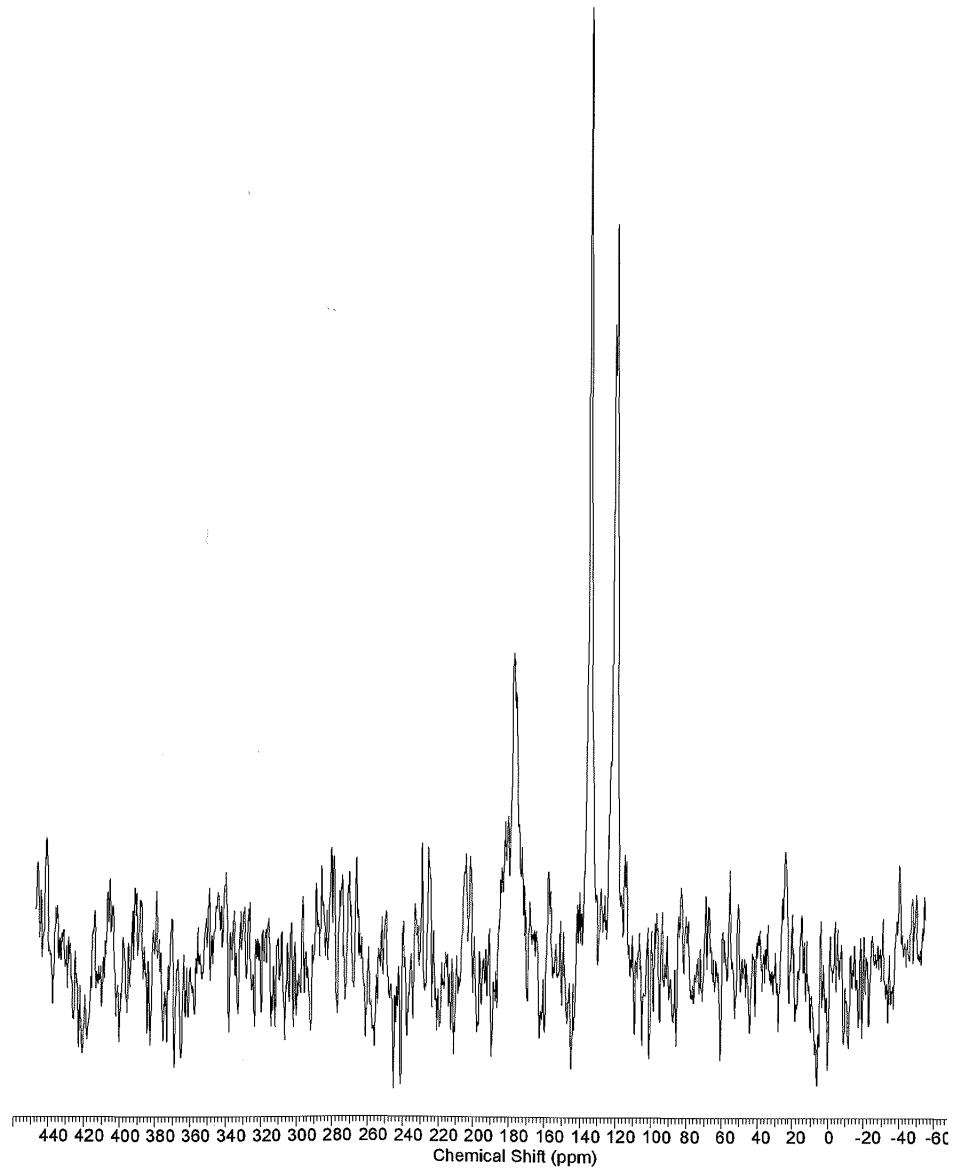
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Figure 3



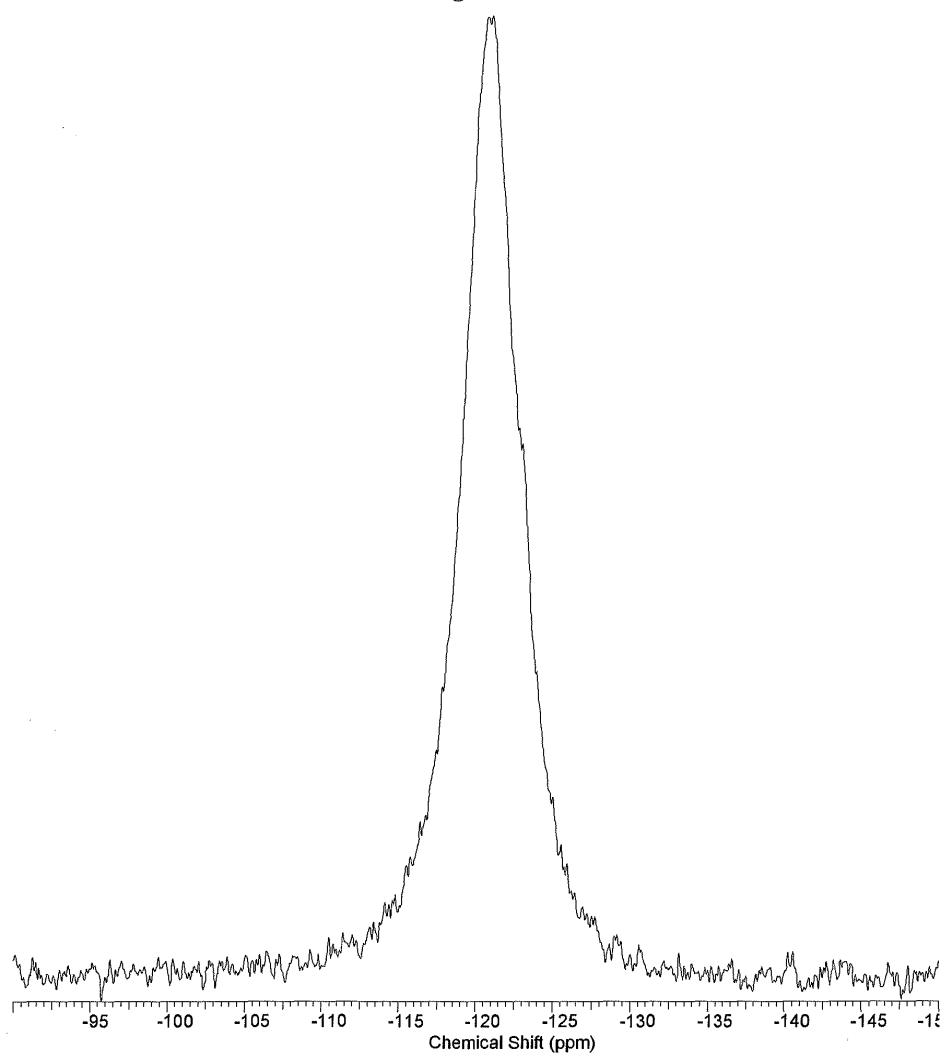
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Figure 4



EXEL2_00132189

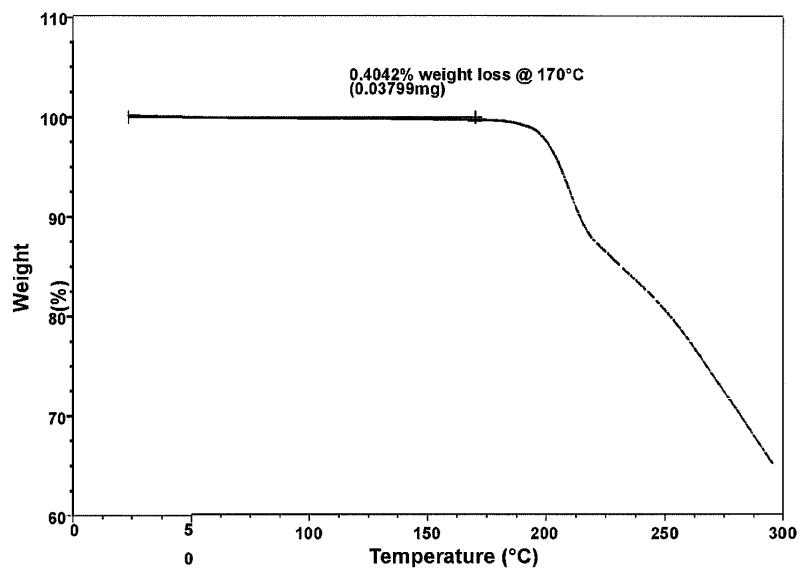
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Figure 5

TGA



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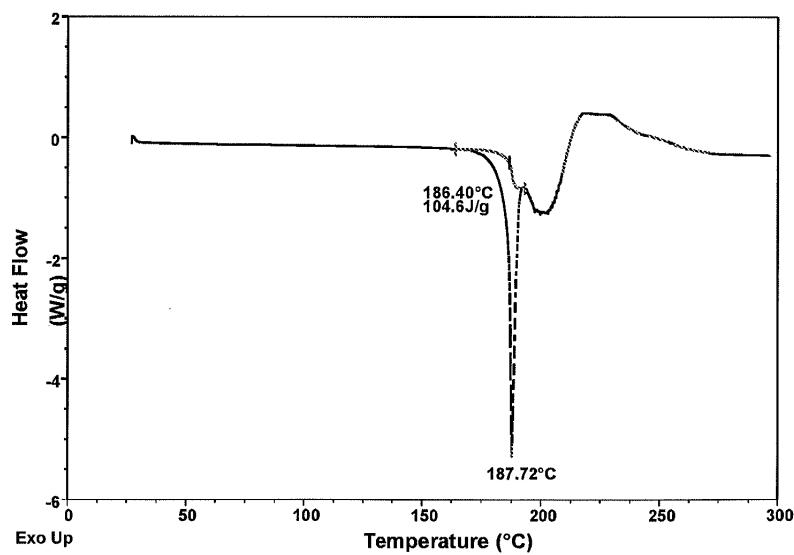
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Figure 6

DSC



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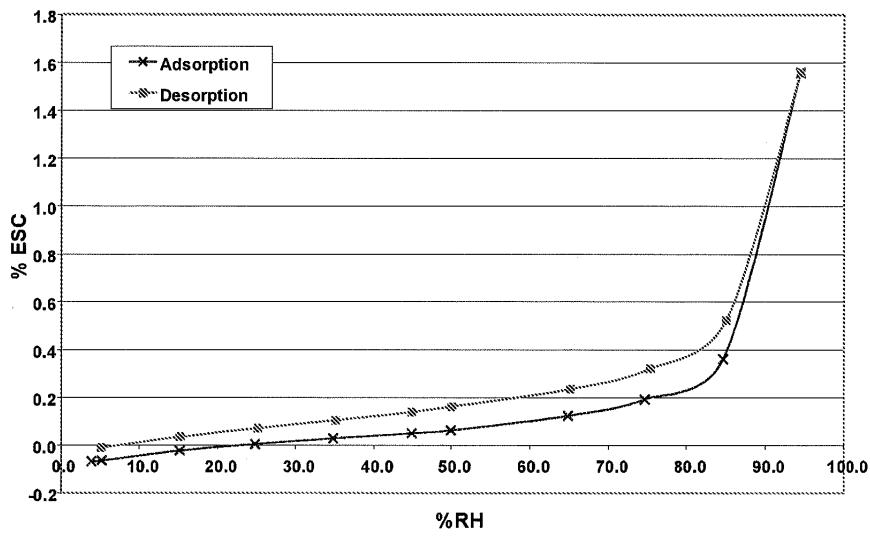
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Figure 7



Moisture Sorption of Compound (I), Form N-1

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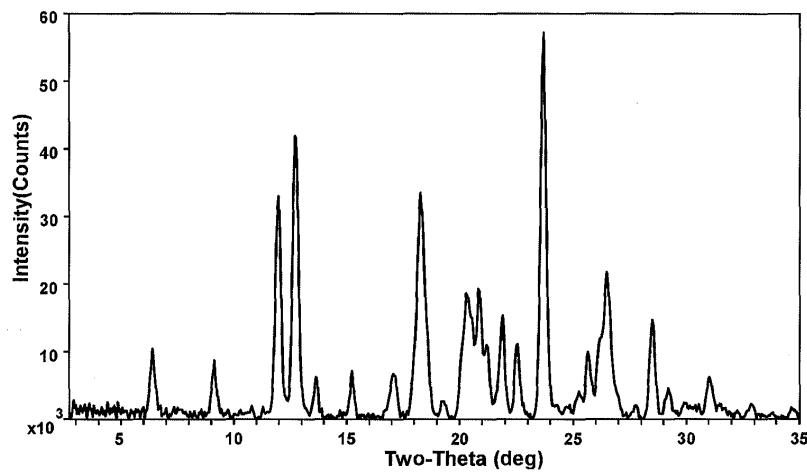
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Figure 8



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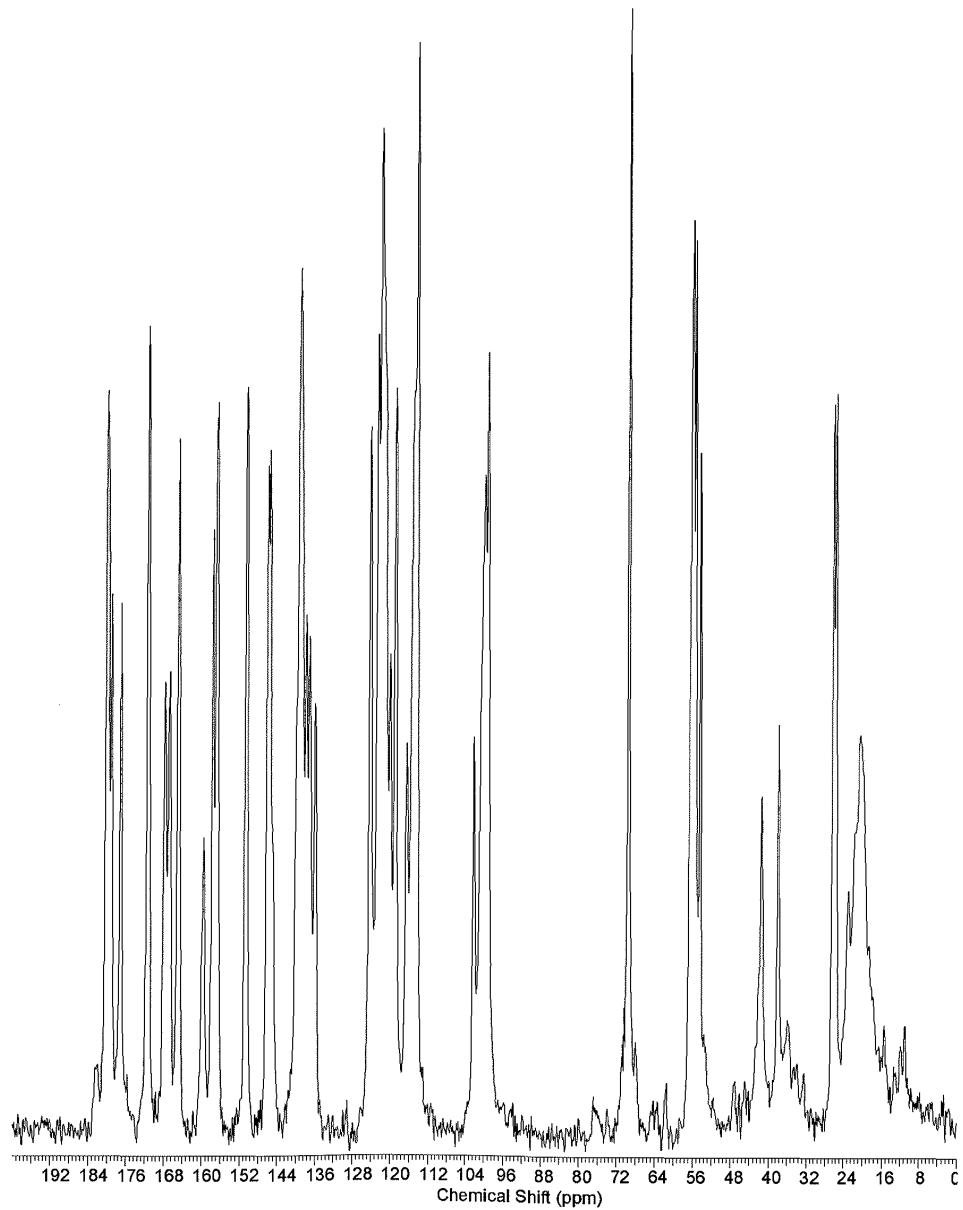
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Figure 9



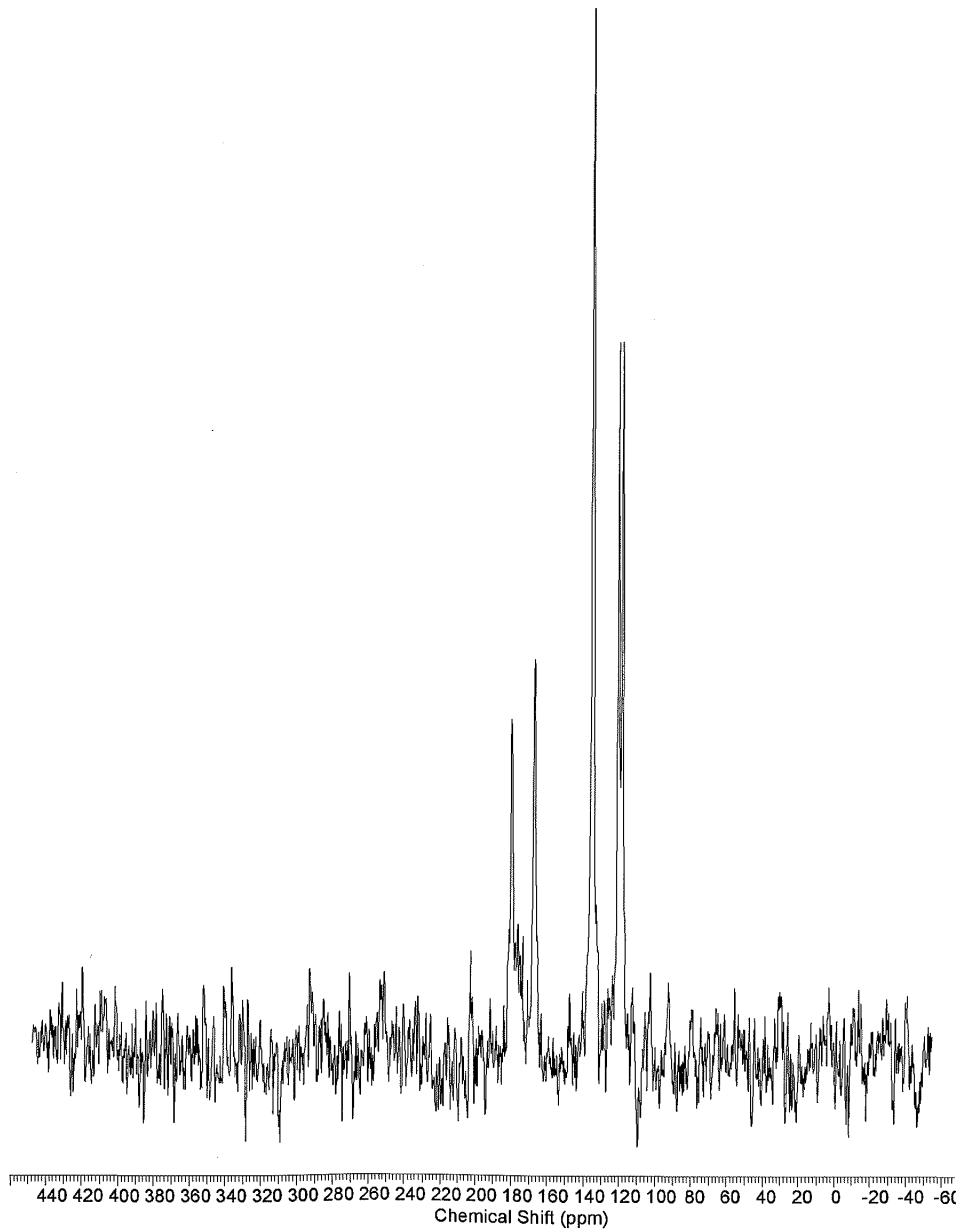
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Figure 10



EXEL2_00132195

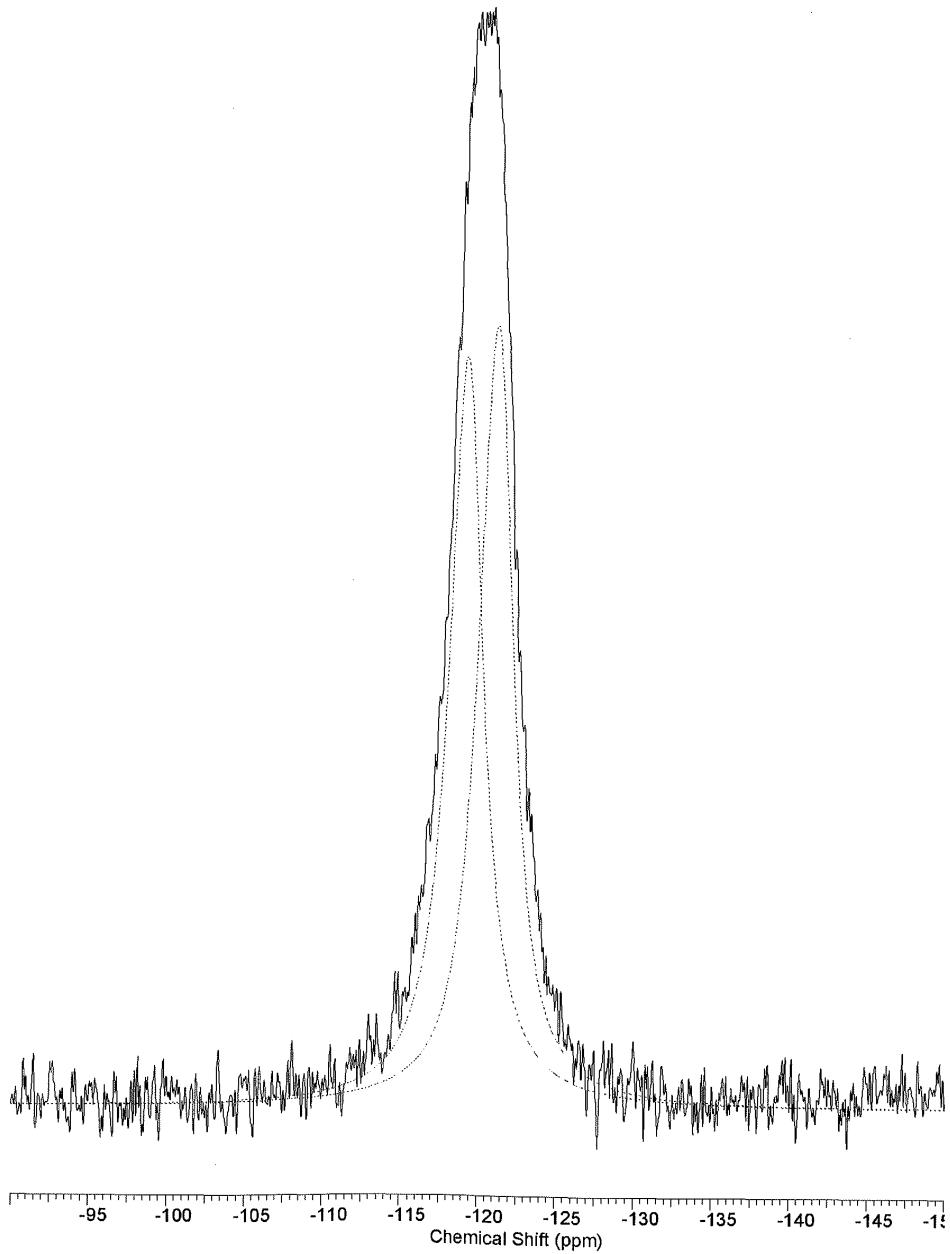
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Figure 11



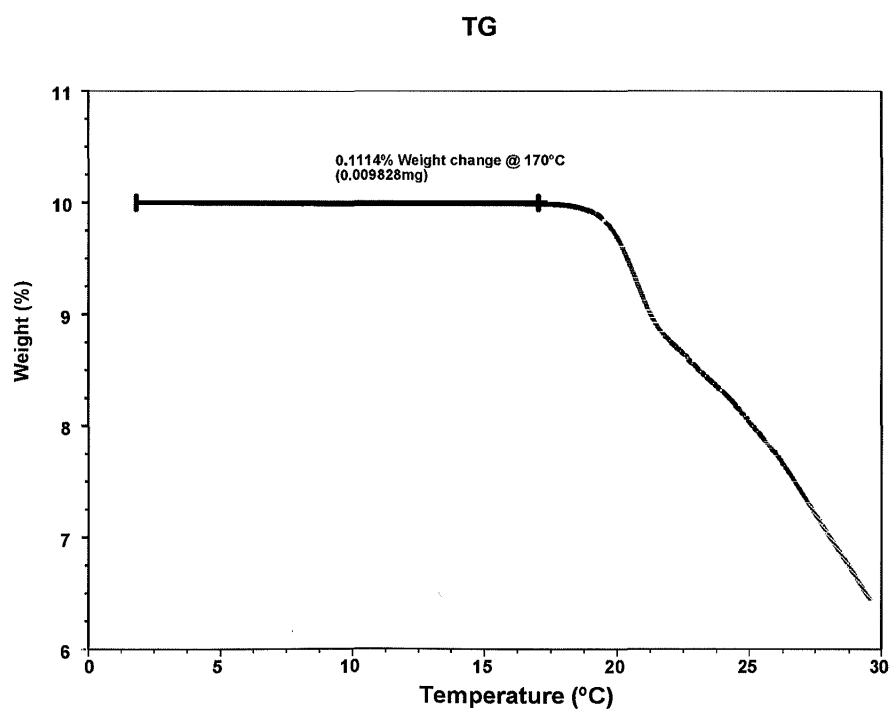
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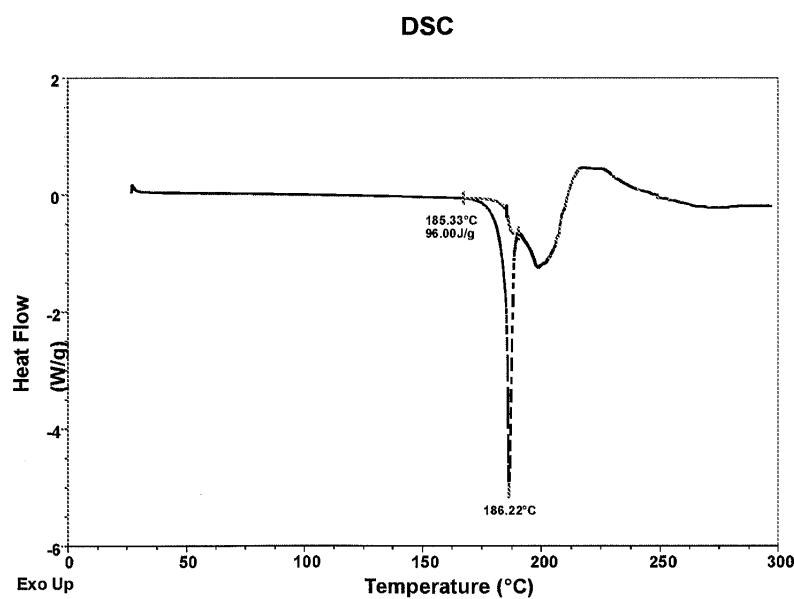
Figure 12



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Figure 13



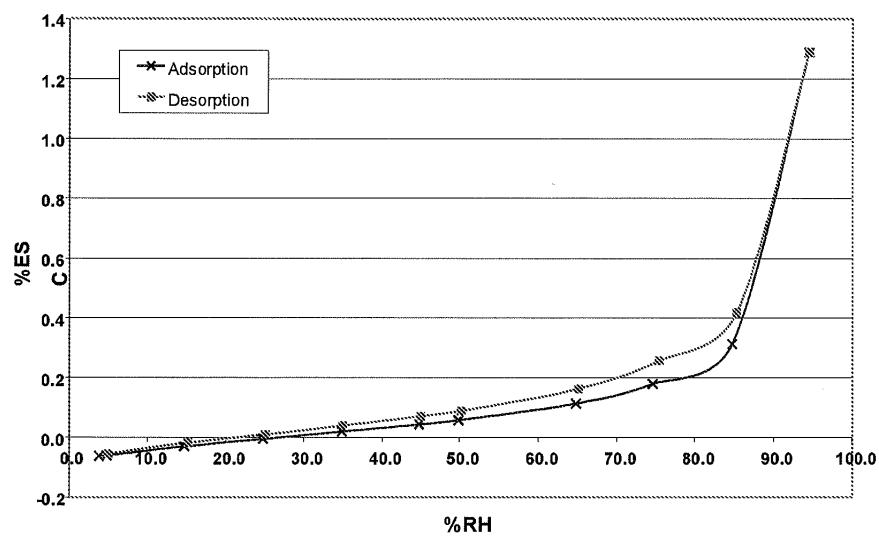
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Figure 14



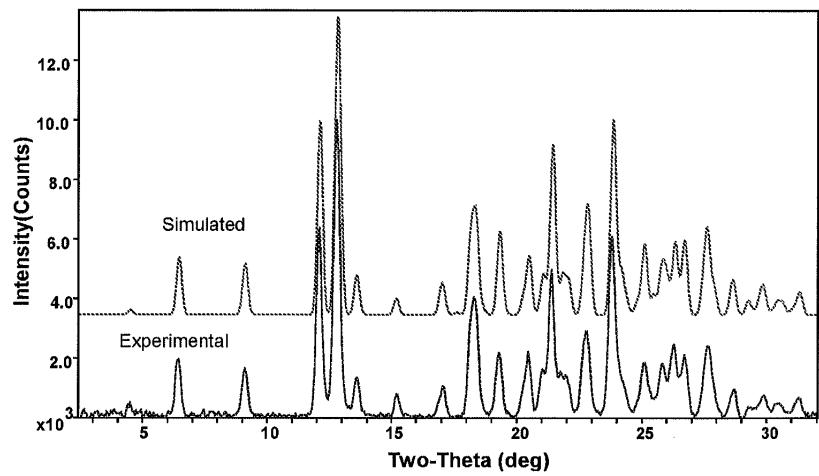
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Figure 15



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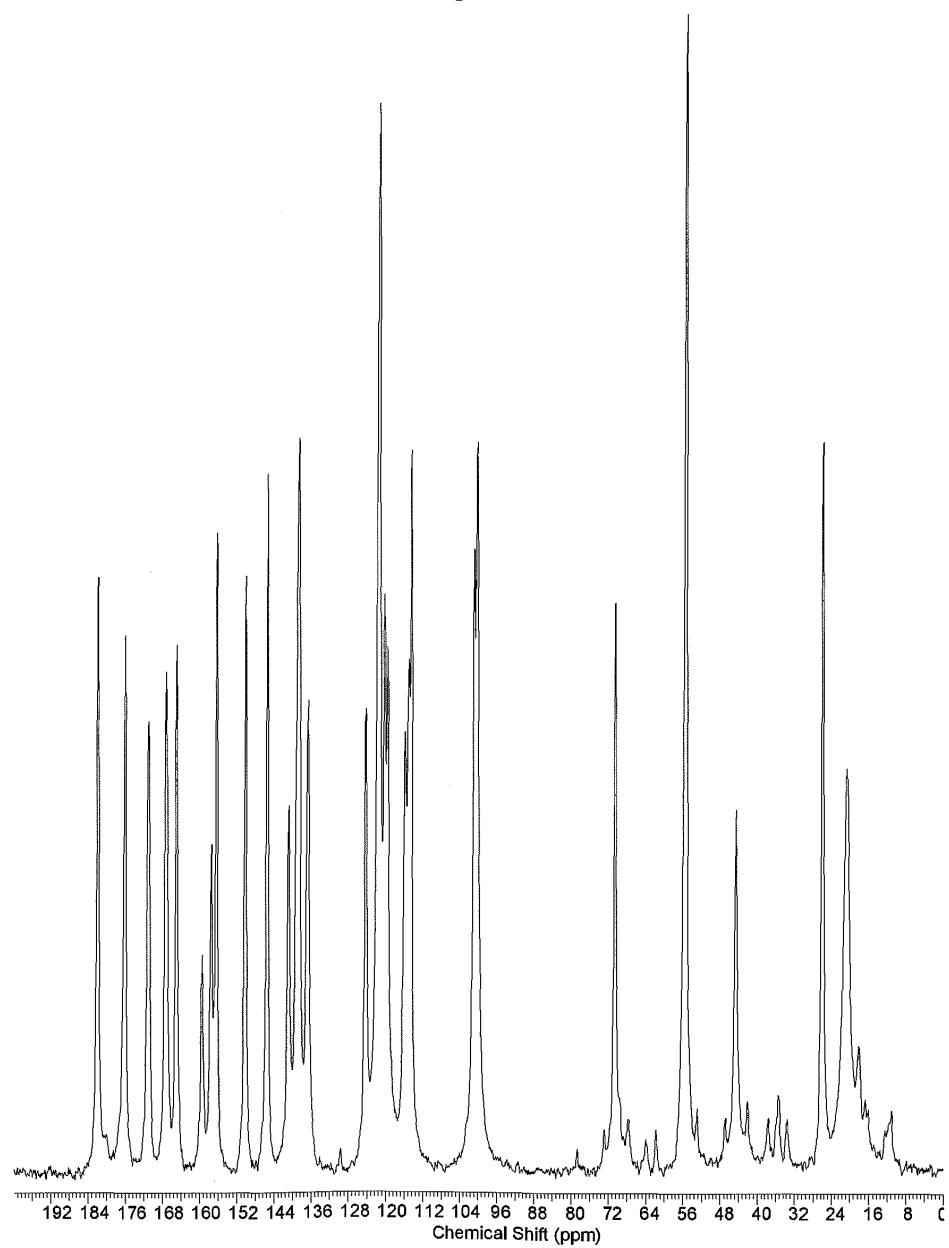
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Figure 16



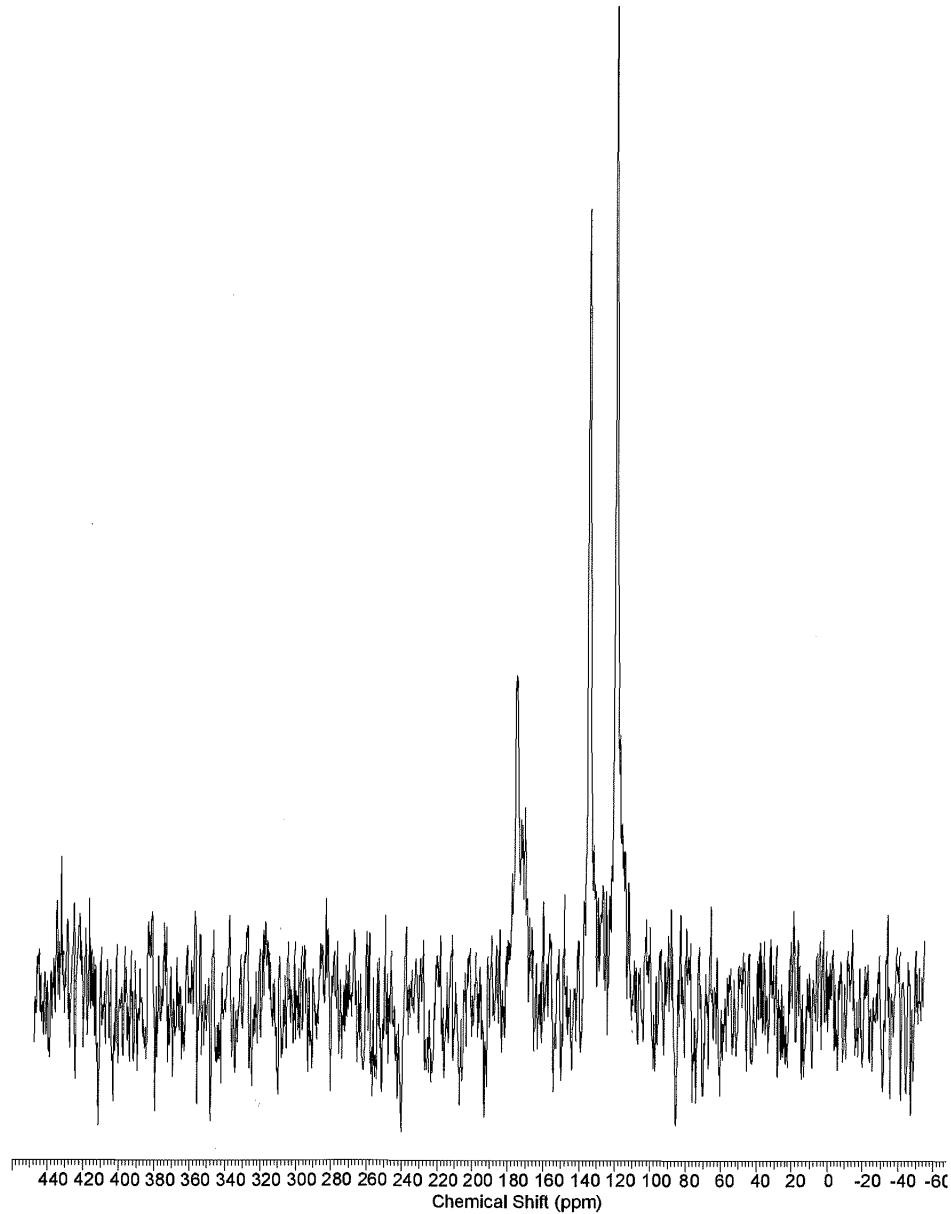
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Figure 17



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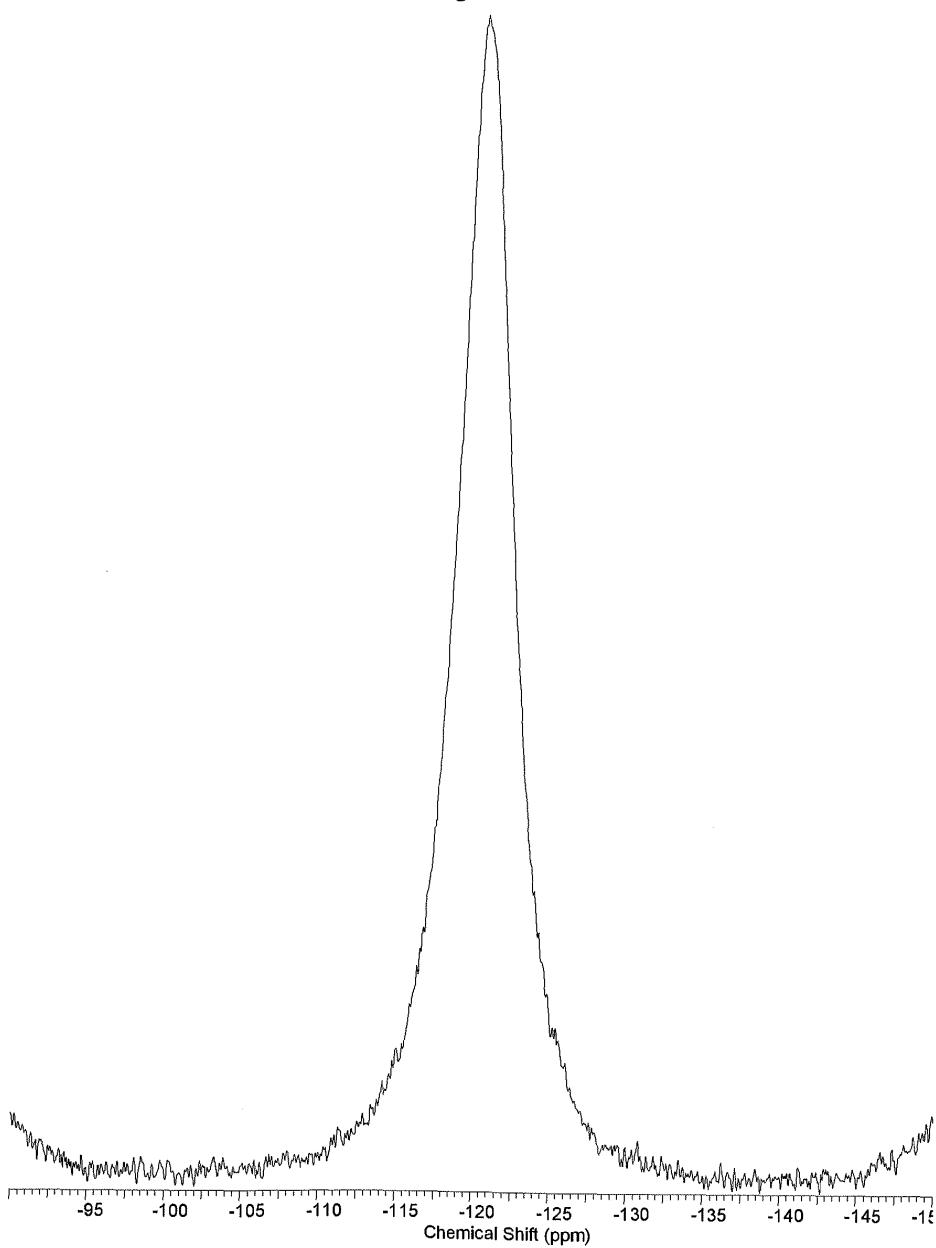
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Figure 18



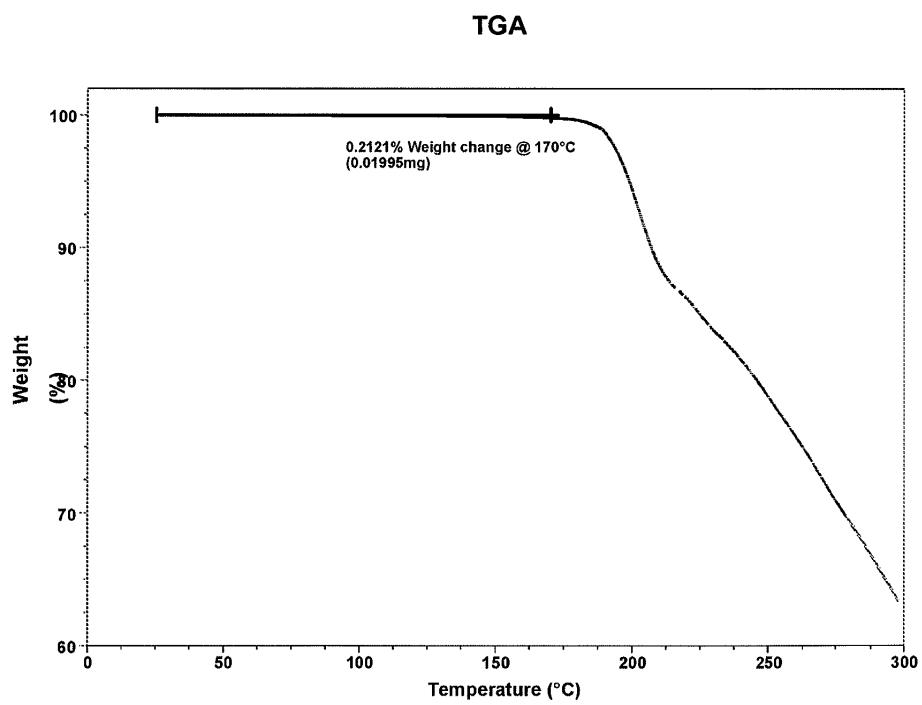
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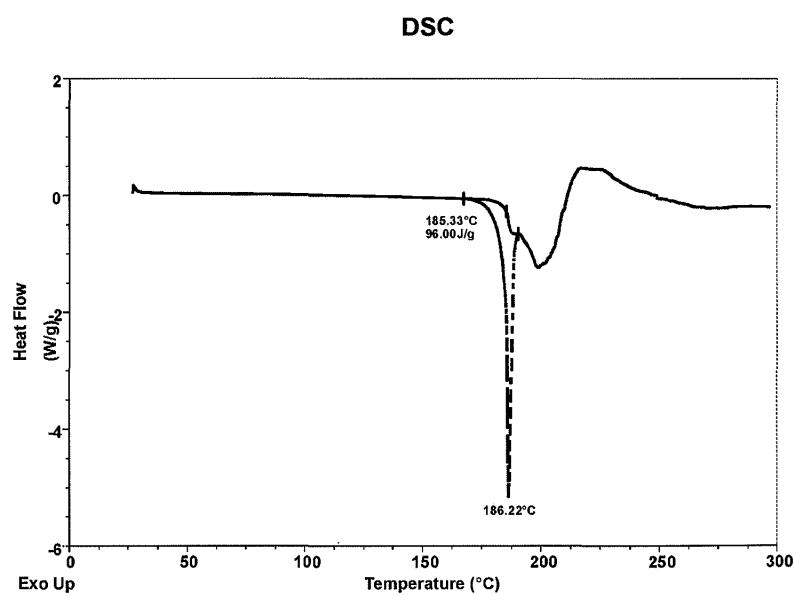
Figure 19



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Figure 20



EXEL2_00132205

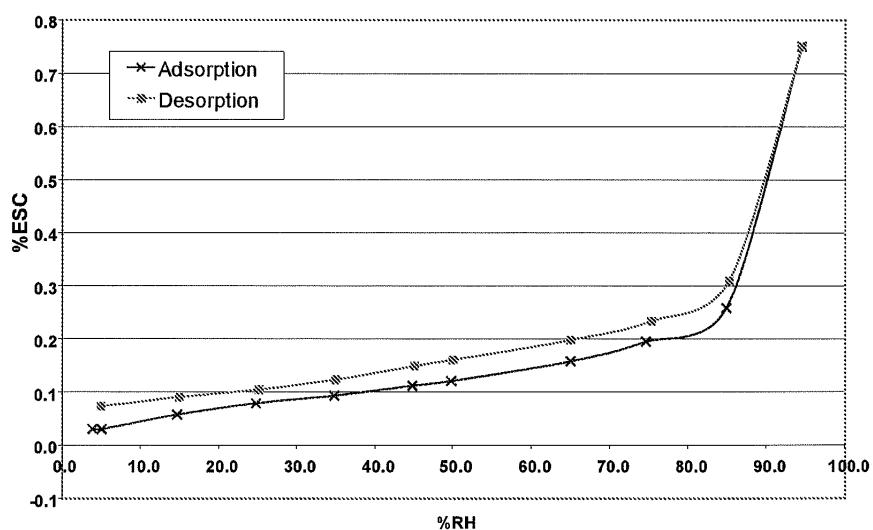
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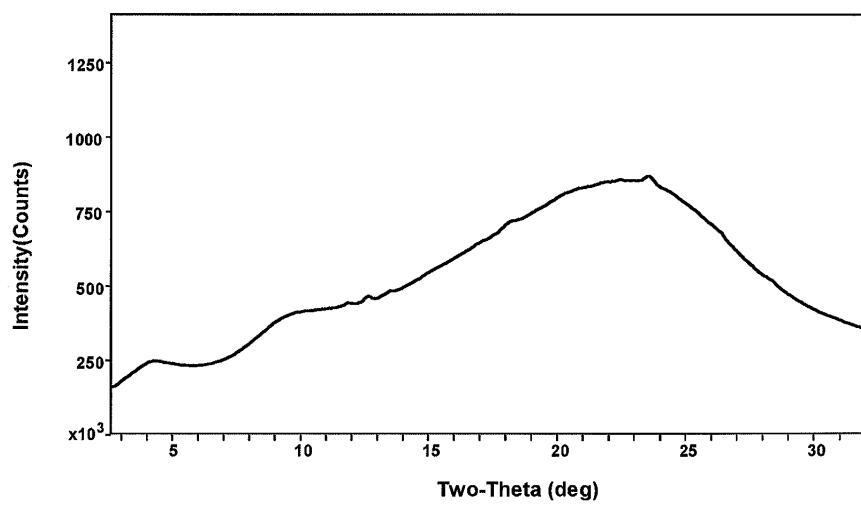
Figure 21



EXEL2_00132206

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Figure 22



EXEL2_00132207

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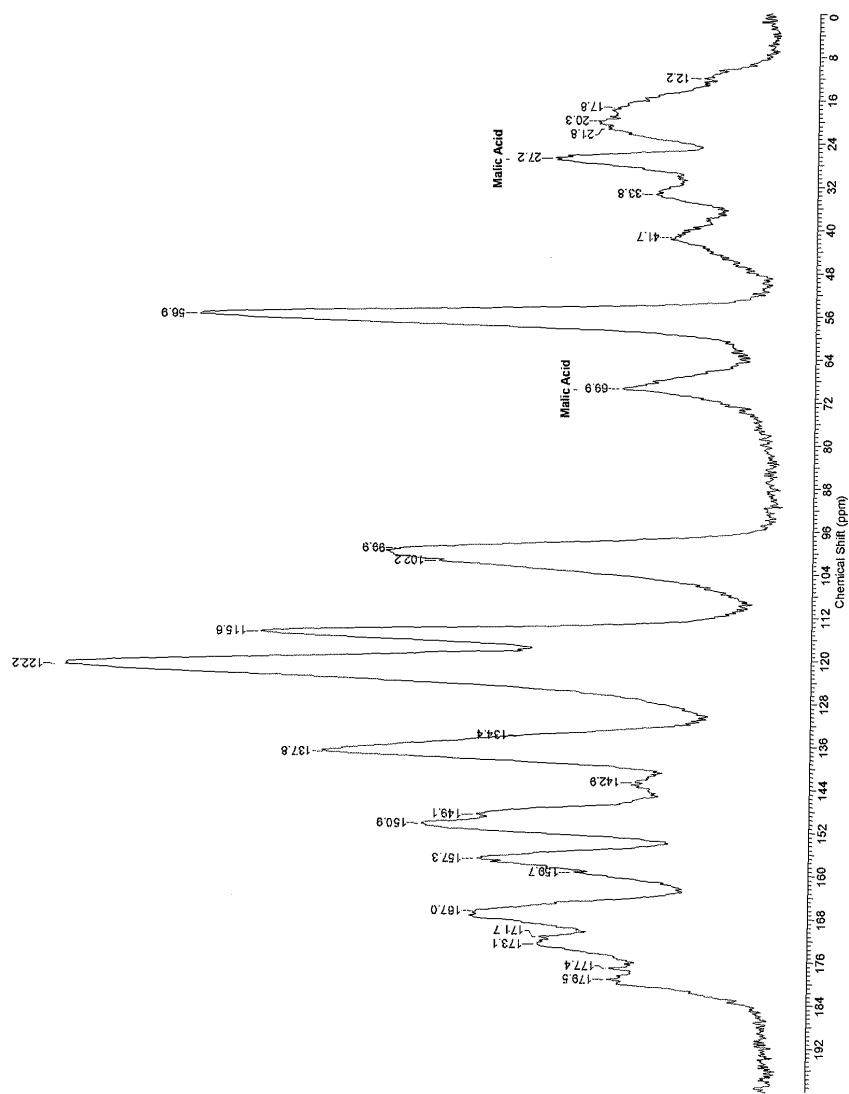


Figure 23

EXEL2_00132208

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Appx121

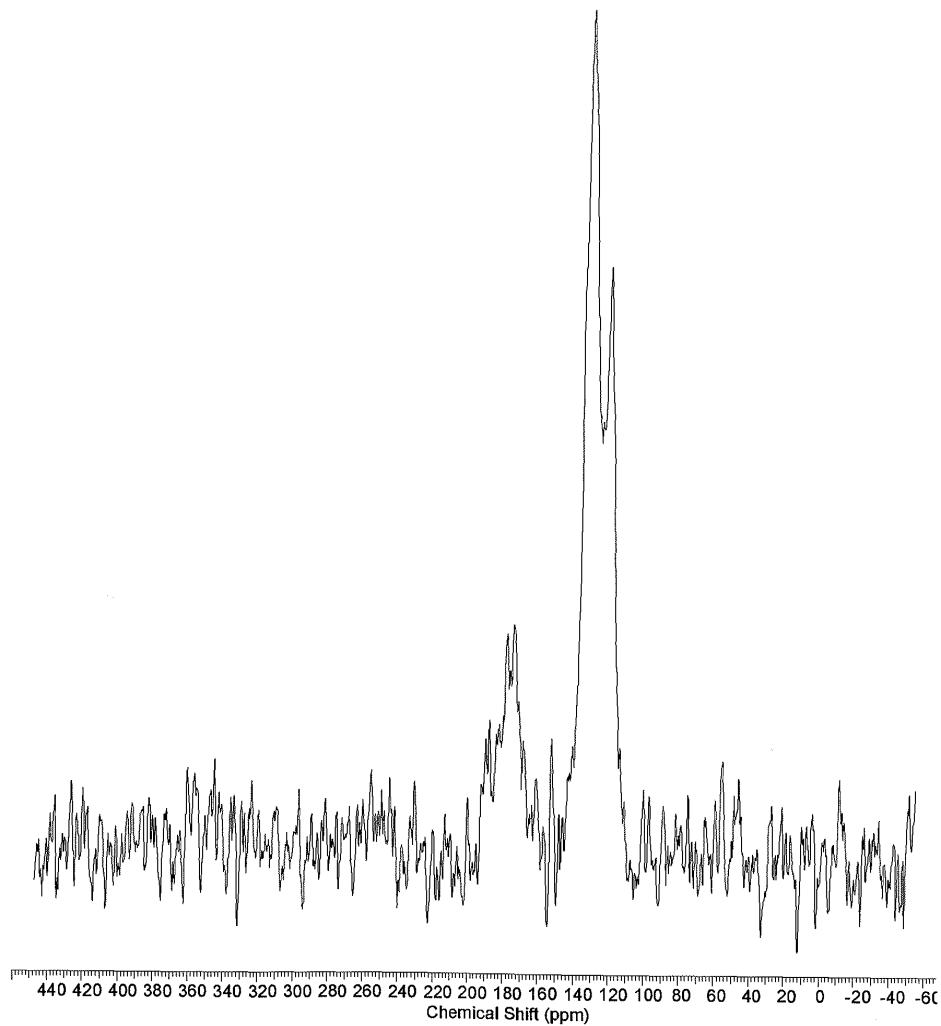
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Figure 24



EXEL2_00132209

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Appx122

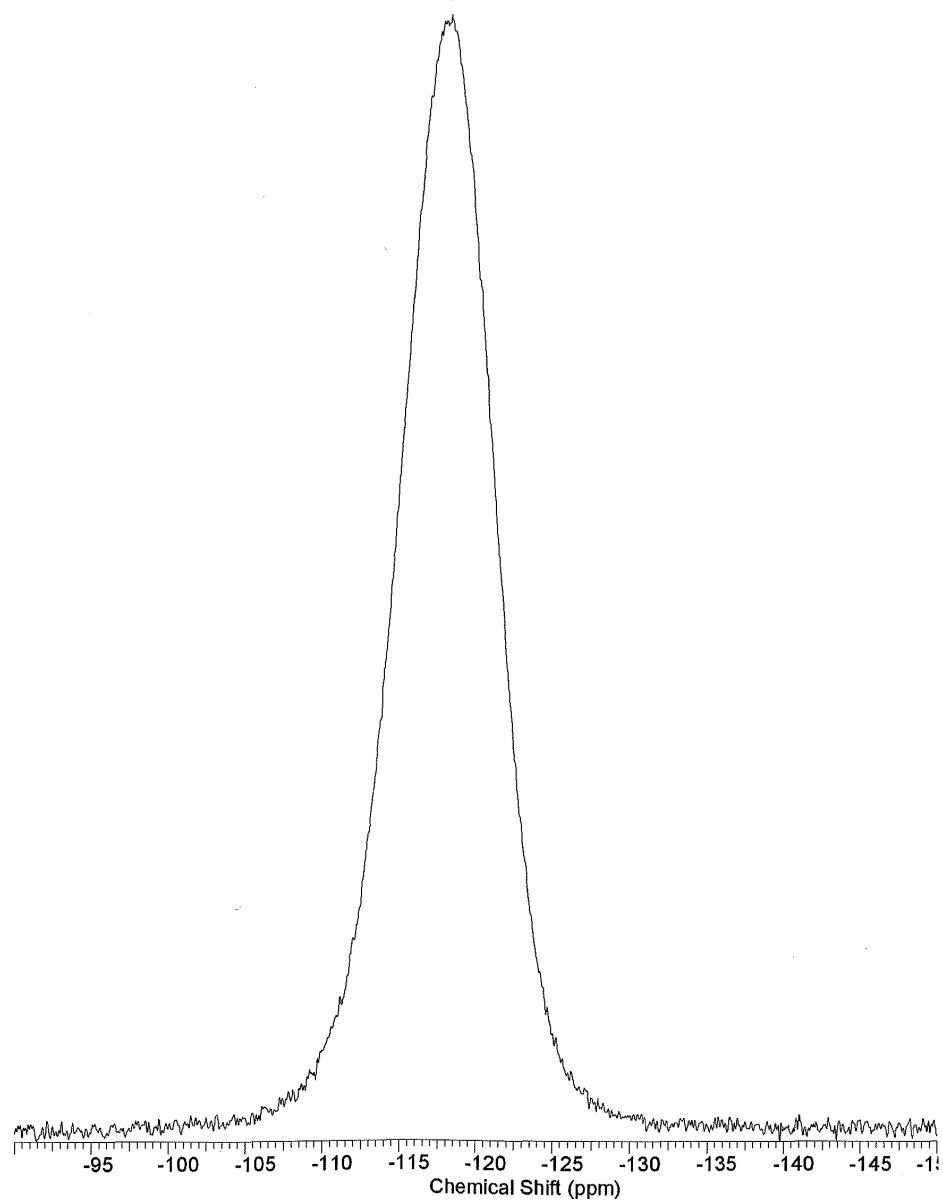
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Figure 25



EXEL2_00132210

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Appx123

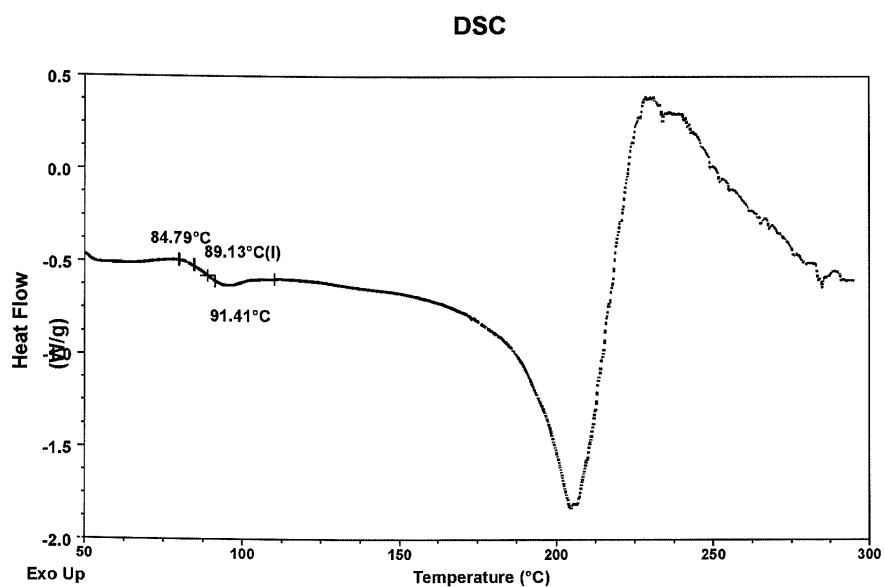
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Figure 26



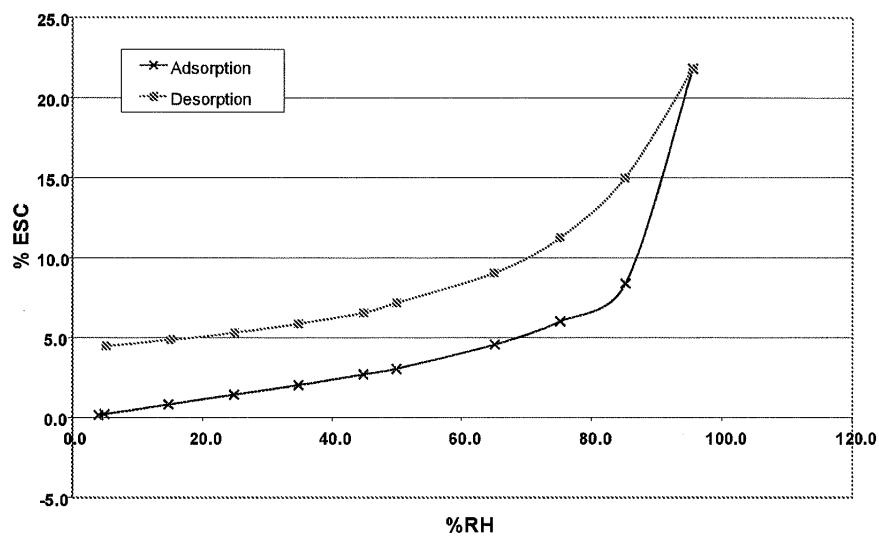
EXEL2_00132211

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Appx124

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Figure 27



EXEL2_00132212

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**MALATE SALT OF
N-(4-[6,7-BIS(METHYLOXY)
QUINOLIN-4-YL]OXY)PHENYL)-N'-(4-
FLUOROPHENYL)CYCLOPROPANE-1,1-
DICARBOXAMIDE, AND CRYSTALLINE
FORMS THEREOF FOR THE TREATMENT
OF CANCER**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation application of U.S. Ser. No. 16/796,250, filed Feb. 20, 2020, which is a continuation application of U.S. Ser. No. 15/617,725, filed Jun. 8, 2017, which is a division of U.S. Ser. No. 14/340,871, filed Jul. 25, 2014, which is a division of U.S. Ser. No. 13/145,054, filed Oct. 20, 2011, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2010/021194, filed Jan. 15, 2010, which claims the benefit of U.S. provisional application No. 61/145,421, filed Jan. 16, 2009, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to malate salts of N-(4-[6,7-bis(methyloxy)-quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and to crystalline and amorphous forms of the malate salts of N-(4-[6,7-bis(methyloxy)-quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. The malate salts of N-(4-[6,7-bis(methyloxy)-quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide include one of (1) the (L)-malate salt, (2) the (D)-malate salt, (3) the (D,L)-malate salt, and (4) mixtures thereof. The disclosure also relates to pharmaceutical compositions comprising at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure also relates to pharmaceutical compositions comprising a crystalline or an amorphous form of at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure also relates to methods of treating cancer comprising administering at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure further relates to methods of treating cancer comprising administering a crystalline or an amorphous form of at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

BACKGROUND

Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

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Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., *DN&P* 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis in vivo (See: Maulik et al *Cytokine & Growth Factor Reviews* 2002 13, 41-59). c-Met, VEGFR2 and/or Ret overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytic tumor (which includes glioblastoma,

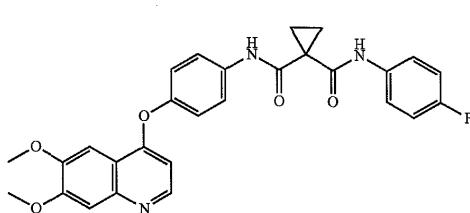
giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components). The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and convert it into an oncogene product.

Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc. Technol.* 20016, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both vascular endothelial growth factor (VEGF) receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc. Technol.* 20016, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition.

Accordingly, small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including Ret, c-Met and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, which has the chemical structure:

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FIG. 10 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-2.

FIG. 11 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-2.

FIG. 12 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-2.

FIG. 13 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-2.

FIG. 14 shows the moisture sorption of crystalline Compound (I), Form N-2.

FIG. 15 shows the experimental and simulated XRPD patterns for crystalline Compound (III), Form N-1 at room temperature.

FIG. 16 shows the solid state ^{13}C NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 17 shows the solid state ^{15}N NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 18 shows the solid state ^{19}F NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 19 shows the thermal gravimetric analysis (TGA) of crystalline Compound (III), Form N-1.

FIG. 20 shows the differential scanning calorimetry (DSC) of crystalline Compound (III), Form N-1.

FIG. 21 shows the moisture sorption of crystalline Compound (III), Form N-1.

FIG. 22 shows the XRPD pattern of amorphous Compound (I) at room temperature.

FIG. 23 shows the solid state ^{13}C NMR spectrum of amorphous Compound (I).

FIG. 24 shows the solid state ^{15}N NMR spectrum of amorphous Compound (I).

FIG. 25 shows the solid state ^{19}F NMR spectrum of amorphous Compound (I).

FIG. 26 shows the differential scanning calorimetry (DSC) of amorphous Compound (I).

FIG. 27 shows the moisture sorption of amorphous Compound (I).

DETAILED DESCRIPTION

This disclosure relates to improvements of the physicochemical properties of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, whereby this compound may be suitable for drug development. Disclosed herein are malate salts of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. New solid state forms of those salts are also disclosed. The malate salts as well as their crystalline and amorphous forms disclosed herein each represent separate aspects of the disclosure. Although the malate salts and their solid state forms are described herein, the invention also relates to novel compositions containing the disclosed salts and solid state forms. Therapeutic uses of the salts and solid state forms described as well as therapeutic compositions containing them represent separate aspects of the disclosure. The techniques used to characterize the salts and their solid state forms are described in the examples below. These techniques, alone or in combination, may be used to characterize the salts and their solid state forms disclosed herein. The salts and their solid state forms may be also characterized by reference to the disclosed figures.

N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide was found to have an enzyme Ret IC₅₀ value of about 5.2 nM (nanomolar) and an enzyme c-Met IC₅₀ value of about 1.3

SUMMARY

This disclosure relates to malate salts of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

Another aspect relates to crystalline and amorphous forms of the malate salts of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the experimental XRPD pattern for crystalline Compound (I), Form N-1 at 25° C.

FIG. 2 shows the solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 3 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 4 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 5 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-1.

FIG. 6 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-1.

FIG. 7 shows the moisture sorption of crystalline Compound (I), Form N-1.

FIG. 8 shows the experimental XRPD pattern for crystalline Compound (I), Form N-2 at 25° C.

FIG. 9 shows the solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-2.

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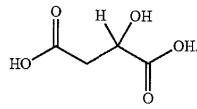
nM (nanomolar). The assay that was used to measure this c-Met activity is described in paragraph [0458] in WO2005-030140.

RET biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described in WO2005-030140. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 2 μ M ATP, 1 μ M poly-EY and 15 nM RET (baculovirus expressed human RET kinase domain M700-D1042 with a (His)₆ tag on the N-terminus) in a 20 μ L assay buffer (20 mM Tris-HCl pH 7.5, 10 mM MgCl₂, 0.01% Triton X-100, 1 mM DTT, 3 mM MnCl₂). The mixture was incubated at ambient temperature for 2 hours after which 20 μ L luciferase-luciferin mix was added and the chemiluminescent signal read using a Wallac Victor² reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5 μ g/mL oxalic acid (pH 7.8), 5 mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μ M AMP, 28 μ g/mL luciferin and 40,000 units of light/nL luciferase.

Malate Salts of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

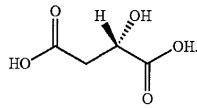
This disclosure relates to malate salts of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. These malate salts are a combination of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide with malic acid which forms a 1:1 malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Malic acid has the following structure:



Due to its chiral carbon, two enantiomers of malic acid exist, (L)-malic acid and (D)-malic acid.

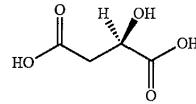
(L)-malic acid has the following structure:



There are various names or designations for the (L)-malic acid that are known in the art. These include butanedioic acid, hydroxy-, (2S)-9CI; butanedioic acid, hydroxy-, (S)-; malic acid, L-(8CI); malic acid, 1-(3CI); (-)-(S)-malic acid; (-)-Hydroxysuccinic acid; (-)-(L)-malic acid; (-)-malic acid; (2S)-2-hydroxybutanedioic acid; (2S)-2-hydroxysuccinic acid; (S)-malic acid; apple acid; L-(-)-malic acid; (L)-malic acid; NSC 9232; S-(-)-malic acid; and S-2-hydroxybutanedioic acid.

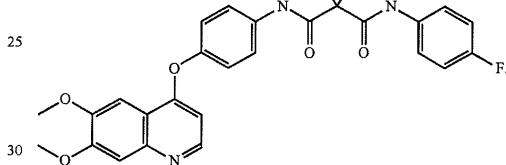
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(D) malic acid has the following structure:



- 5 There are various names or designations for the (D)-malic acid that are known in the art. These include butanedioic acid, 2-hydroxy-, (2R)-, butanedioic acid, hydroxy-, (2R)-9CI; butanedioic acid, hydroxy-, (R)-; (+)-malic acid; (2R)-2-hydroxybutanedioic acid; (2R)-malic acid; (R)-(+)-malic acid; (R)-malic acid; D-(+)-2-hydroxysuccinic acid; D-(+)-malic acid; and D-malic acid.

As discussed above, the chemical structure of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is



25 There are no chiral carbons in its chemical structure. There are various names for N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide which are publicly known, and some of these various names or designations include 1,1-cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- and 1,1-cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)-(9CI).

30 N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide can be prepared according to any of several different methodologies, either on a gram scale (<1 kg) or a kilogram scale (>1 kg). A gram-scale method is set forth in WO 2005-030140, which describes the synthesis of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Examples 25, 37, 38, and 48), which is hereby incorporated by reference. Alternatively, N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including the active compound (s), can be prepared on a kilogram scale using the procedure set forth in Example 1 below.

35 This disclosure relate to malate salts of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide:
the (L)-malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound I);
the (D)-malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound II); and
the (DL)-malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Compound III).

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Each has improved properties over N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and its other salts. The names used herein to characterize a specific form, e.g. "N-2" etc., are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics, but rather such names are used as mere identifiers that are to be interpreted in accordance with the characterization information presented herein.

The malate salts of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, and particularly Compound (I), have a preferred combination of pharmaceutical properties for development. Under the conditions of 25° C./60% relative humidity (RH) and 40° C./60% RH, Compound (I) showed no change in assay, purity, moisture and dissolution. The DSC/TGA showed the Compound (I) to be stable up to 185° C. No solvent losses were observed. The uptake of water by the (L)-malate salt was reversible with a slight hysteresis. The amount of water taken up was calculated at about 0.60 wt % at 90% RH. The (L)-malate salt was synthesized with good yield and purity >90% and had sufficient solubility for use in a pharmaceutical composition. The amount of water associated with this salt was calculated at about 0.5 wt % by Karl Fischer analysis and correlates with TGA and GVS analysis. The (D)-malate salt of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide will have the same properties as the (L)-malate salt of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of the N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. For example, the hydrochloride salt of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide exhibits undesirable moisture sensitivity, changing phase upon exposure to high humidity (75% humidity) and high temperature (40° C.). The maleate salt had low solubility. The tartrate salt had low crystallinity and low solubility. The phosphate salt exhibited an 8% weight gain due to absorption of H₂O—the highest among the salts tested.

The water solubility of the various salts was determined using 10 mg solids per mL water. The salts were prepared in a salt screen by reacting an acetone solution of the freebase with stock tetrahydrofuran (THF) solutions of a range of acids in about a 1:1 molar ratio. Table 1 below summarizes the water solubility and other data relating to the free base and each salt.

TABLE 1

	Solubility (mg/ml)	
Free base	<<0.001	very low solubility
Propionate	<<0.001	no salt formation; mixture of free base and acid
Acetate	<<0.001	no salt formation; mixture of free base and acid
Succinate	0.010	no salt formation; mixture of free base and acid
Benzoate	0.005	no salt formation; mixture of free base and acid
L-Lactate	0.015	Amorphous salt
Pyroglutamate	0.44	Amorphous salt
Glycolate	0.016	Amorphous, salt low crystallinity
L-Ascorbate	0.053	
Sulfate	0.004	Crystalline salt, low solubility

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TABLE 1-continued

	Solubility (mg/ml)	
Tosylate	0.007	Crystalline salt, low solubility
Malonate	<<0.003	Crystalline salt, low solubility
2,5-dihydroxybenzoate	<<0.001	Crystalline Salt, low solubility
Fumarate	0.008	Crystalline Salt, low solubility
Citrate	0.002	Crystalline Salt, low solubility
Mesylate	0.175	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Esylate	0.194	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Benzenesulfonate	0.039	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Chloride	0.070	Crystalline but Hygroscopic; possible hydrate formation. Change in XRPD pattern upon exposure to humidity.
Maleate	0.005	Crystalline salt, possible hydrate formation; low solubility; different XRPD pattern observed upon scale up (possible polymorphism issue)
Phosphate	0.026	Crystalline but Hygroscopic.
L-Tartrate	0.014	Low degree of crystallinity; Hygroscopic.
(L)-Malate	0.059	Crystalline; non-Hygroscopic with no indication of hydrate formation. Suitable solubility, and chemical/physical stability.

Another aspect of this disclosure relates to crystalline forms of Compound (I), which include the N-1 and/or the N-2 crystalline form of Compound (I) as described herein. Each of form of Compound (I) is a separate aspect of the disclosure. Similarly, another aspect of this disclosure relates to crystalline forms of Compound (II), which include the N-1 and/or the N-2 crystalline form of Compound (II) as described herein. Each of which is also a separate aspect of the disclosure. As is known in the art, the crystalline (D) malate salt will form the same crystalline form and have the same properties as crystalline Compound (I). See WO 2008/083319, which discusses the properties of crystalline enantiomers. Mixtures of the crystalline forms of Compounds (I) and (II) are another aspect of the disclosure.

The crystalline N-1 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

- (i) a solid state ¹³C NMR spectrum with peaks at 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1 ppm, 0.2 ppm;
 - (ii) a solid state ¹³C NMR spectrum substantially in accordance with the pattern shown in FIG. 2;
 - (iii) an x-ray powder diffraction pattern (CuK α $\lambda=1.5418 \text{ \AA}$) comprising four or more peaks selected from: 6.4, 9.0, 12.0, 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6° $\pm 0.2^\circ$, wherein measurement of the crystalline form is at an ambient room temperature;
 - (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 1;
 - (v) a solid state ¹⁵N NMR spectrum with peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm; and/or
 - (vi) a solid state ¹⁵N NMR spectrum substantially in accordance with the pattern shown in FIG. 3.
- Other solid state properties which may be used to characterize the crystalline N-1 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below. For crystalline Compound (I), the solid state phase and the degree of crystallinity remained unchanged after exposure to 75% RH at 40° C. for 1 week.

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The crystalline N-2 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

- (i) a solid state ^{13}C NMR spectrum with peaks at 23.0, 25.9, 38.0, 54.4, 56.11, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ± 0.2 ppm;
- (ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. 9;
- (ii) an x-ray powder diffraction pattern ($\text{CuK}\alpha \lambda=1.5418 \text{\AA}$) comprising four or more peaks selected from: 6.4, 9.1, 12.0, 12.8, 13.7, 17.1, 20.9, 21.9, 22.6, and $23.7^{\circ}20\pm 0.2^{\circ}20$, wherein measurement of the crystalline form is at an ambient room temperature;
- (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 8;
- (v) a solid state ^{15}N NMR spectrum with peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm; and/or
- (vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. 10.

Other solid state properties which may be used to characterize the crystalline N-2 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below.

In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-1 form.

In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-2 form.

The disclosure also relates to amorphous forms of Compounds (I) and (II). The preparation and solid state properties and characteristics of the amorphous form of Compound (I) are described in the examples below. The amorphous forms of Compounds (I) and (II) represent another aspect of the disclosure.

One further aspect of the disclosure relates to mixtures of Compound (I) and Compound (II). The mixtures may have from greater than zero weight % to less than 100 weight % Compound (I) and from less than 100 weight % to greater zero weight % Compound (II), based on the total weight of Compound (I) and Compound (II). In other embodiments, the mixture comprises from about 1 to about 99 weight % Compound (I) and from about 99 to about 1 weight % Compound (II), based on the total weight of Compound (I) and Compound (II) in said mixture. In a further embodiment, the mixture comprises from about 90 weight % to less than 100 weight % Compound (I) and from greater than zero weight % to about 10 weight % Compound (II), based on the total weight of Compound (I) and Compound (II). Accordingly, the mixture may have 1-10% by weight of Compound (I); 11-20% by weight of Compound (I); 21-30% by weight of Compound (I); 31-40% by weight of Compound (I); 41-50% by weight of Compound (I); 51-60% by weight of Compound (I); 61-70% by weight of Compound (I); 71-80% by weight of Compound (I); 81-90% by weight of Compound (I); or 91-99% by weight of Compound (I) with the remaining weight percentage of malate salt being that of Compound (II).

Another aspect of this disclosure relates to crystalline forms of (DL)-malate salt of N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, Compound (III). The (DL)-malate salt is prepared from racemic malic acid. The crystalline N-1

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form of Compound (III) as described here may be characterized by at least one of the following:

- (i) a solid state ^{13}C NMR spectrum with four or more peaks selected from 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, 182.1 ppm, ± 0.2 ppm;
- (ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. 16;
- (iii) a powder x-ray diffraction pattern ($\text{CuK}\alpha \lambda=1.5418 \text{\AA}$) comprising four or more 2 θ values selected from: 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6, $\pm 0.2^{\circ}20$, wherein measurement of the crystalline form is at temperature of room temperature;
- (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 15;
- (v) a solid state ^{15}N NMR spectrum with peaks at 119.6, 134.7, and 175.5 ppm, ± 0.2 ppm; and/or
- (vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. 17.

Other solid state properties which may be used to characterize the crystalline N-1 form of Compound (III) are shown in the figures and discussed in the examples below. In one embodiment, the N-1 Form of Compound (III) is characterized by unit cell parameters approximately equal to the following:

Cell dimensions: $a=14.60 \text{\AA}$

$b=5.20 \text{\AA}$

$c=39.09 \text{\AA}$

$\alpha=90.0^\circ$

$\beta=90.4^\circ$

$\gamma=90.0^\circ$

Space group: $P2_1/h$

Molecules of Compound (I)/unit cell: 4

Volume= 2969\AA^3

Density (calculated)= 1.422 g/cm^3

The unit cell parameters of Form N-1 of Compound (III) were measured at a temperature of approximately 25°C , e.g., ambient or room temperature.

Each of the N-1 and N-2 crystalline forms of Compounds (T) and (IT) and the crystalline form N-1 of Compound (III) have unique characteristics that can distinguish them one from another. These characteristics can be understood by comparing the physical properties of the solid state forms which are presented in the Examples below. For example, Table 2 lists characteristic XRPD peak positions ($^{\circ}20\pm 0.2^{\circ}20$) for crystalline Compound (III), Form N-1 and Forms N-1 and N-2 of crystalline Compound (I). Amorphous forms do not display reflection peaks in their XRPD patterns.

TABLE 2

Characteristic diffraction peak positions (degrees $2\theta \pm 0.2$) @ RT, based on pattern collected with a diffractometer ($\text{CuK}\alpha$) with a spinning capillary.

Compound (I) Form N-1	Compound (I) Form N-2	Compound (III) Form N-1
6.4	6.4	6.4
9.0	9.1	9.1
12.0	12.0	12.1
12.8	12.8	12.8
13.5	13.7	13.6
16.9	17.1	17.1
19.4*	20.9*	19.3
21.5*	21.9*	21.4
22.8*	22.6	22.8

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TABLE 2-continued

Characteristic diffraction peak positions (degrees $2\theta \pm 0.2$) @ RT, based on pattern collected with a diffractometer (CuK α) with a spinning capillary.

Compound (I) Form N-1	Compound (I) Form N-2	Compound (III) Form N-1
25.1*	23.7	25.1
27.6*	—	27.6

*unique reflections between Compound (I), Form N-1 and Compound (I), Form N-2.

The unique reflections between Forms N-1 and N-2 of crystalline Compound (II) are designated by an asterisk (*). As discussed above, Compound (II) is an enantiomer of Compound (I) and thus, Compound (II), Form N-1 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-1. Likewise, Compound (II), Form N-2 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-2. Compounds (I) and (II) are distinct from one another based on their absolute stereochemistry, i.e., the (L)-malate salt versus the (D)-malate salt, respectively. Crystalline Compound (III), Form N-1, is distinct as the (D,L)-malate salt.

The characteristic peaks from the solid state NMR may also serve to distinguish the crystalline and amorphous forms disclosed herein. For example, Table 3 lists characteristic solid state ^{13}C NMR peaks for crystalline Compound (III), Form N-1; crystalline Compound (I), Forms N-1 and N-2, and the amorphous form of Compound (I).

TABLE 3

Solid State Carbon-13 NMR Resonances (ppm, ± 0.2 ppm)			
(I), Form N-1	(I), Form N-2	(III), Form N-1	(I), Amorphous
18.1	23.0	20.8	97.2
42.9	25.9	26.2	33.8
44.5	38.0	44.8	142.9
54.4	54.4	70.7	—
56.1	56.1	114.7	—
70.4	41.7	141.1	—
123.2	69.7	145.7	—
156.2	102.0	176.3	—
170.8	122.5	182.1	—
175.7	177.3	—	—
182.1	179.3	—	—
—	180.0	—	—
—	180.3	—	—

The solid state ^{19}F and N NMR spectra, discussed below, provide data for similar comparison and characterization. As discussed above, being an enantiomer of Compound (I), crystalline Forms N-1 and N-2 and the amorphous form of Compound (II) will have the same solid state NMR resonances, and unique peaks between them, as those listed in Table 3 for Forms N-1 and N-2 of crystalline Compound (I). Pharmaceutical Compositions and Methods of Treatment

Another aspect of this disclosure relates to a pharmaceutical composition comprising at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient. The amount of Compound (I), Compound (II), Compound (III), or the combinations thereof in the pharmaceutical composition can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may individually be present in the pharmaceutical composition as one of the solid state forms discussed above or combinations thereof. The crys-

talline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a solid or dispersion pharmaceutical composition comprising at least one of a therapeutically effective amount of a crystalline form of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient.

Another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or Compound (III) may be administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms, with crystalline Compound (I), Form N-1 or N-2 being preferred. Accordingly another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, the method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (I), Compound (I), Compound (I) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer (including astrocytic tumor, which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components), lung cancer (including non-small cell lung cancer), bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, lymphoma, solid tumors, Hodgkin's disease, non-Hodgkin's lymphoma or thyroid cancer thyroid cancer (including medullary thyroid cancer).

Tyrosine kinase inhibitors have also been used to treat non-small cell lung cancer (NSCLC). Gefitinib and erlotinib are angiogenesis inhibitors that target receptors of an epidermal growth factor called tyrosine kinase. Erlotinib and Gefitinib are currently being used for treating NSCLC. Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]-phenyl)-N⁴-[4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof, optionally in combination with Erlotinib or Gefitinib. In another embodiment, the combination is with Erlotinib.

Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating a method of treating non-small cell lung cancer

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(NSCLC) in a subject, the method comprising administering to the subject in need of the treatment therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (I), Compound (II), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. In another embodiment, the combination administered in this method is Erlotinib with at least one of Compound (I), Compound (II), Compound (I), or combinations thereof.

Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating an astrocytic tumor comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (I), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof. The amount administered can be a therapeutically effective amount.

Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating thyroid cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In

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another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms.

Accordingly another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (U), Compound (III) or combinations thereof such as discussed above. Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, a crystalline form of Compound (I), Compound (II), or any combination of Compound (I) and (II). The amount of Compound (I), Compound (II), or any combination of Compound (I) and (II) administered can be a therapeutically effective amount.

Another aspect of this disclosure relates to a use of the N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate salt according to any of the above embodiments for the manufacture of a medicament for the treatment of a disease or disorder discussed above. When dissolved, a crystalline or amorphous form according to this disclosure loses its solid state structure, and is therefore referred to as a solution of, for example, Compound (I). At least one crystalline form disclosed herein may be used to prepare at least one liquid formulation in which at least one crystalline form according to the disclosure is dissolved and/or suspended.

A pharmaceutical composition such as discussed above may be any pharmaceutical form which contains active Compound (I), Compound (II) and/or Compound (III), including the solid state forms thereof (hereinafter referred to as active compound(s)). The pharmaceutical composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. The pharmaceutical compositions generally contain about 1% to about 99% by weight of the active compound(s), or a crystalline form of the active compound(s), and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of active compound, with the rest being suitable pharmaceutical excipients or other adjuvants, as discussed below.

A "therapeutically effective amount of the active compounds, or a crystalline or amorphous form of the active compound(s), according to this disclosure to inhibit, regulate and/or modulate the signal transduction of kinases (discussed here concerning the pharmaceutical compositions)

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refers to an amount sufficient to treat a patient suffering from any of a variety of cancers associated with abnormal cell proliferation and angiogenesis. A therapeutically effective amount according to this disclosure is an amount therapeutically useful for the treatment or prevention of the disease states and disorders discussed herein. Compounds (I), (II), and/or (III) (including their solid state forms), possess therapeutic activity to inhibit, regulate and/or modulate the signal transduction of kinases such as described in WO2005-030140. N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

The actual amount required for treatment of any particular patient will depend upon a variety of factors including the disease state being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex and diet of the patient; the mode of administration; the time of administration; the route of administration; and the rate of excretion of the active compound(s), or a crystalline form of the active compound(s), according to this disclosure; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J. Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference. The active compound(s), or a crystalline form of active compound(s), according to this disclosure and pharmaceutical compositions comprising them, may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. They may also be co-formulated with one or more of such agents in a single pharmaceutical composition.

Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends partly upon the desired method of administration to be used. For a pharmaceutical composition of this disclosure, that is, one of the active compound(s), or a crystalline form of the active compound(s), of this disclosure, a carrier should be chosen so as to substantially maintain the particular form of the active compound(s), whether it would be crystalline or not. In other words, the carrier should not substantially alter the form the active compound(s) are. Nor should the carrier be otherwise incompatible with the form of the active compound(s), such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

The pharmaceutical compositions of this disclosure may be prepared by methods known in the pharmaceutical formulation art, for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). In a solid dosage forms Compound (I) is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for

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example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of this disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. If desired, a pharmaceutical composition of this disclosure may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and antioxidants, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, and butylated hydroxytoluene.

Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the active compound(s), or a crystalline form of the active compound(s), with, for example, suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

Because the active compound(s), or a crystalline form of the active compound(s), is maintained during their preparation, solid dosage forms are preferred for the pharmaceutical composition of this disclosure. Solid dosage forms for oral administration, which includes capsules, tablets, pills, powders, and granules, are particularly preferred. In such solid dosage forms, the active compound(s) mixed with at least one inert, pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier). Administration of the active compound(s), or a crystalline form of the active compound(s), in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravescically, intracisternally, or rectally, in the form of

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solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. One preferable route of administration is oral administration, using a convenient dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

General Preparation Methods of Crystalline Forms

Crystalline forms may be prepared by a variety of methods including, but not limited to, for example, crystallization or recrystallization from a suitable solvent mixture; sublimation; growth from a melt; solid state transformation from another phase; crystallization from a supercritical fluid; and jet spraying. Techniques for crystallization or recrystallization of crystalline forms of a solvent mixture include, but are not limited to, for example, evaporation of the solvent; decreasing the temperature of the solvent mixture; crystal seeding of a supersaturated solvent mixture of the compound and/or salt thereof; crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof; freeze drying the solvent mixture; and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S. R. Bym, R. R. Pfeiffer, and J. G. Stowell, 2nd Edition, SSCI, West Lafayette, Ind. (1999).

In a crystallization technique in which solvent is employed, the solvent(s) are typically chosen based on one or more factors including, but not limited to, for example, solubility of the compound; crystallization technique utilized; and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution to which antisolvent is then added to decrease the solubility of the Compound (I) in the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

In one method that can be used in preparing crystals, Compound (I), Compound (II) and/or Compound (III) can be suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed Cooling Batch Crystallizers," J. W. Mullin and J. Nyvlt, Chemical Engineering Science, 1971, 26, 3690377. In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing large crystals, or by microcrystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

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A cooled crystallization mixture may be filtered under vacuum and the isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization solvent. After being washed, the product may be dried under a nitrogen purge to afford the desired crystalline form. The product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, for example, differential scanning calorimetry (DSC); x-ray powder diffraction (XRPD); and thermogravimetric analysis (TGA) to assure the crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 wt. % isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 wt. % isolated yield. Optionally, the product may be delumped by being comilled or passed through mesh screen.

The features and advantages of this disclosure may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of this disclosure that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof. The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference. All measurements are subject to experimental error and are within the spirit of the invention.

As used herein, "amorphous" refers to a solid form of a molecule and/or ion that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern with sharp maxima.

As used herein, the term "substantially pure" means the crystalline form of Compound (I) referred to contains at least about 90 wt. % based on the weight of such crystalline form. The term "at least about 90 wt. %," while not intending to limit the applicability of the doctrine of equivalents to the scope of the claims, includes, but is not limited to, for example, about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99 and about 100% wt. %, based on the weight of the crystalline form referred to. The remainder of the crystalline form of Compound (I) may comprise other Form(s) of Compound (I) and/or reaction impurities and/or processing impurities that arise, for example, when the crystalline form is prepared. The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectroscopy, and/or infrared spectroscopy.

PREPARATIVE EXAMPLES

Example 1: Preparation of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate Salt Thereof (Compound (I))

The synthetic route used for the preparation of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-(4-fluoro-

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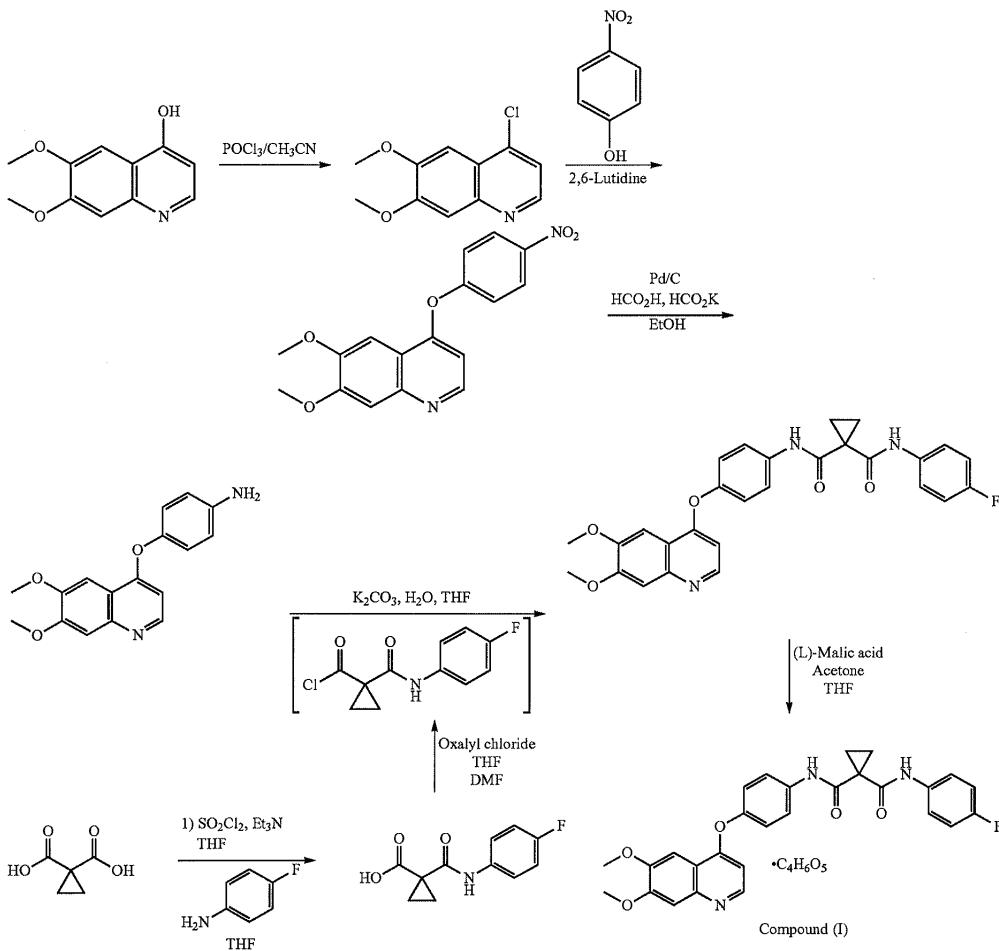
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phenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 1:

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quenched into a chilled solution of dichloromethane (DCM, 238.0 kg), 30% NH₄OH (135.0 kg), and ice (440.0 kg). The

SCHEME 1



The process shown in Scheme 1 is described in more detail below.

1.1 Preparation of 4-chloro-6,7-dimethoxy-quinoline

A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (1 L, 10.0 kg) and acetonitrile (64.0 L). The resulting mixture was heated to approximately 65° C. and phosphorus oxychloride (POCl₃, 50.0 kg) was added. After the addition of POCl₃, the temperature of the reaction mixture was raised to approximately 80° C. The reaction was deemed complete (approximately 9.0 hours) when <2% of the starting material remained (in process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 10° C. and then

resulting mixture was warmed to approximately 14° C., and phases were separated. The organic phase was washed with water (40.0 kg) and concentrated by vacuum distillation with the removal of solvent (approximately 190.0 kg). Methyl-t-butyl ether (MTBE, 50.0 kg) was added to the batch, and the mixture was cooled to approximately 10° C., during which time the product crystallized out. The solids were recovered by centrifugation, washed with n-heptane (20.0 kg), and dried at approximately 40° C. to afford the title compound (8.0 kg).

1.2 Preparation of 6,7-Dimethyl-4-(4-nitro-phenoxy)-quinoline

A reactor was sequentially charged with 4-chloro-6,7-dimethoxy-quinoline (8.0 kg), 4 nitrophenol (7.0 kg), 4

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dimethylaminopyridine (0.9 kg), and 2,6 lutidine (40.0 kg). The reactor contents were heated to approximately 147° C. When the reaction was complete (<5% starting material remaining as determined by in process HPLC analysis, approximately 20 hours), the reactor contents were allowed to cool to approximately 25° C. Methanol (26.0 kg) was added, followed by potassium carbonate (3.0 kg) dissolved in water (50.0 kg). The reactor contents were stirred for approximately 2 hours. The resulting solid precipitate was filtered, washed with water (67.0 kg), and dried at 25° C. for approximately 12 hours to afford the title compound (4.0 kg).

**1.3 Preparation of
4-(6,7-Dimethoxy-quinoline-4-yloxy)-phenylamine**

A solution containing potassium formate (5.0 kg), formic acid (3.0 kg), and water (16.0 kg) was added to a mixture of 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline (4.0 kg), 10% palladium on carbon (50% water wet, 0.4 kg) in tetrahydrofuran (40.0 kg) that had been heated to approximately 60° C. The addition was carried out such that the temperature of the reaction mixture remained approximately 60° C. When the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining, typically 15 hours), the reactor contents were filtered. The filtrate was concentrated by vacuum distillation at approximately 35° C. to half of its original volume, which resulted in the precipitation of the product. The product was recovered by filtration, washed with water (12.0 kg), and dried under vacuum at approximately 50° C. to afford the title compound (3.0 kg; 97% AUC).

1.4 Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid

Triethylamine (8.0 kg) was added to a cooled (approximately 4° C.) solution of commercially available cyclopropane-1,1-dicarboxylic acid (21, 10.0 kg) in THF (63.0 kg) at a rate such that the batch temperature did not exceed 10° C. The solution was stirred for approximately 30 minutes, and then thionyl chloride (9.0 kg) was added, keeping the batch temperature below 10° C. When the addition was complete, a solution of 4-fluoroaniline (9.0 kg) in THF (25.0 kg) was added at a rate such that the batch temperature did not exceed 10° C. The mixture was stirred for approximately 4 hours and then diluted with isopropyl acetate (87.0 kg). This solution was washed sequentially with aqueous sodium hydroxide (2.0 kg dissolved in 50.0 L of water), water (40.0 L), and aqueous sodium chloride (10.0 kg dissolved in 40.0 L of water). The organic solution was concentrated by vacuum distillation followed by the addition of heptane, which resulted in the precipitation of solid. The solid was recovered by centrifugation and then dried at approximately 35° C. under vacuum to afford the title compound. (10.0 kg).

**1.5 Preparation of
1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride**

Oxalyl chloride (1.0 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (2.0 kg) in a mixture of THF (11 kg) and N, N-dimethylformamide (DMF; 0.02 kg) at a rate such that the batch temperature did not exceed 30° C. This solution was used in the next step without further processing.

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1.6 Preparation of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

The solution from the previous step containing 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride was added to a mixture of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (3.0 kg) and potassium carbonate (4.0 kg) in THF (27.0 kg) and water (13.0 kg) at a rate such that the batch temperature did not exceed 30° C. When the reaction was complete (in typically 10 minutes), water (74.0 kg) was added. The mixture was stirred at 15-30° C. for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a premade solution of THF (11.0 kg) and water (24.0 kg), and dried at approximately 65° C. under vacuum for approximately 12 hours to afford the title compound (free base, 5.0 kg). ¹H NMR (400 MHz, d₆-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15 (m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LCMS: M+H=502.

1.7 Preparation of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L) malate salt (Compound (I))

A solution of (L)-malic acid (2.0 kg) in water (2.0 kg) was added to a solution of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide free base (15, 5.0 kg) in ethanol, maintaining a batch temperature of approximately 25° C. Carbon (0.5 kg) and thiol silica (0.1 kg) were then added, and the resulting mixture was heated to approximately 78° C., at which point water (6.0 kg) was added. The reaction mixture was then filtered, followed by the addition of isopropanol (38.0 kg), and was allowed to cool to approximately 25° C. The product was recovered by filtration and washed with isopropanol (20.0 kg) and dried at approximately 65° C. to afford Compound (I) (5.0 kg).

Example 2: Preparation of Crystalline Compound (I), Form N-1

A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60° C. and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

At 60° C., acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60° C. for 10 hours. The solution was then cooled to 20° C. and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR; 1.20 L). The solids were dried at 60° C. (25 mm 11 g) for 6 hours to afford Compound (I), Form N-1 (108 g; 0.85 equiv; 108.00 g; 85.22% yield) as a white crystalline solid.

Example 3: Alternate Preparation of Crystalline Compound (I), Form N-1

A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next,

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20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 h with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

Separately, a powder blend was made with known amounts of two batches of Compound (I): (1) 300 mg of batch 1, which contained approximately 41% Compound (I), Form N-1 and 59% Compound (1), Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to Compound (I), Form N-2.

The Compound (I), Form N-1 and Compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45° C. to afford 128 mg of crystalline Compound (1) in the N-1 form.

Example 4: Preparation of Crystalline Compound (I), Form N-2

4.1 Preparation of Crystalline Compound (I), Form N-2 Seed Crystals

A solution was prepared by combining 20 ml of acetone and 300 mg of freebase N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide in a 25 ml screw capped vial. Next, 0.758 ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hr at ambient temperature. The sample was then suction filtered with 0.45 µm PTFE filter cartridge and dried in vacuo at ambient temperature overnight.

4.2 Preparation of Crystalline Compound (I), Form N-2

To a reactor were added N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50° C. Seed crystals were added (1% 480 mg) and the malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 mL/min (3 h)). The slurry was held at 50° C. for 18 h and then was cooled to 25° C. over 30 min. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL). The solids were dried under vacuum at 60° C. for 5 h to afford Compound (I) (55.7 g; 0.92 equiv; 55.70 g; 91.56% yield) as an off-white crystalline solid.

Example 5: Preparation of Crystalline Compound (III), Form N-1

A one mL aliquot (DL)-malic acid salt of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, slurried in tetrahydro-

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furan (THF), was heated to 60° C. on a hot-plate in a half-dram vial. Next, tetrahydrofuran was added drop-wise until an almost clear solution was obtained. The vial was capped, removed from the hot plate and equilibrated at ambient temperature without agitation. Crystallization was apparent after several hours and the solution was allowed to stand overnight to allow completion. Several droplets of the resulting slurry were placed on a glass slide for microscopic analysis. The crystalline material consisted of many elongated plates ranging up to 60 microns in the longest dimension.

Alternate Preparation of Crystalline Compound (III), Form N-1

To a reactor were added N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (15 g; 1.00 equiv; 15.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (DL)-malic acid (1.2 equiv (molar); 4.53 g) was dissolved into methyl isobutyl ketone (8 mL/g-bulk-LR; 120.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 15.00 mL). Next, 20 nL of the solution was added to the first solution at 50° C. The malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 mL/min (3 h)). The slurry was held at 50° C. for 18 h and then was cooled to 25° C. over 30 min. The solids were filtered, and washed with 20% THF/MIBK (0V, 150 mL). The solids were dried under vacuum at 60° C. for 5 h to afford Compound (III) (15.52 g; 86.68% yield) as an off-white solid.

Example 6: Preparation of Amorphous Compound (I)

A solution was prepared with 5 g of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate and 250 nL of a 1:1 (v:v) mixture of methanol and dichloromethane. The hazy solution was filtered through a 0.45 micron filter to yield a clear, yellowish solution. The solution was pumped through the spray dryer nozzle at a rate of 12.9 cc/min, and was atomized by nitrogen gas fed at a rate of 10.911 min. The temperature at the inlet of the cyclone was set to 65° C. to dry the wet droplets. Dry amorphous powder (1.5 g) was collected (yield=30%).

CHARACTERIZATION EXAMPLES

I. NMR Spectra in Dimethyl Sulfoxide Solution

I.1 Compound (I), Form N-1

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, 1H, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (400 MHz, d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

I.2 Compound (I), Form N-2

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, J=5 Hz, 1H), 7.12-7.19 (m, 2H),

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7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

I.3 Compound (III), Form N-1

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

Characterization of Solid State Forms of N-(4-{[6, 7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate

II. Powder X-Ray Diffraction (XRPD) Studies

X-Ray Powder Diffraction (XRPD) patterns were collected on a Bruker AXS C2 GADDS diffractometer equipped with an automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. The radiation source used was copper (Cu K α =1.5406 Å), wherein the voltage was set at 40 kV and the current was set at 40 mA, X-ray optics consists of a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm. The beam divergence, i.e. the effective size of the X-ray beam on the sample, was approximately 4 mm. A θ-θ continuous scan mode was employed with a sample-detector distance of 20 cm which gives an effective 2θ range of 3.2°-29.8°. Samples run under ambient conditions (from about 18° C. to about 25° C.) were prepared as flat plate specimens using powder as received without grinding. Approximately 1-2 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. Typically the sample would be exposed to the X-ray beam for 120 seconds. Beam divergence (i.e., effective size of X-ray spot, gives a value of approximately 4 mm. Alternatively, the powder samples were placed in sealed glass capillaries of 1 mm or less in diameter; the capillary was rotated during data collection at a sample-detector distance of 15 cm. Data were collected for 3≤2θ≤35° with a sample exposure time of at least 2000 seconds. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional XRPD pattern with a step size of 0.02°2θ in the range of 3 to 35°2θ±0.2°2θ. The software used for data collection was GADDS for WNT 4.1.16 and the data were analyzed and presented using Diffrac Plus EVA v 9.0.0.2 or v 13.0.0.2.

II.1 Compound (I), Form N-1

FIG. 1 shows the experimental XRPD pattern of crystalline Compound (I), Form N-1 acquired at room temperature (about 25° C.). A list of the peaks are shown in Table 2, above. The 2θ values at 19.4, 21.5, 22.8, 25.1, and 27.6 (±0.2°2θ) are useful for characterizing crystalline Compound (I), Form N-1. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

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II.2 Compound (I), Form N-2

FIG. 8 shows the experimental XRPD pattern of crystalline Compound (I), Form N-2 acquired at room temperature (about 25° C.). A list of the peaks are shown in Table 2, above. The 2θ values at 20.9 and 21.9 (±0.2°2θ) are useful for characterizing crystalline Compound (I), Form N-2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-2.

II.3 Compound (III), Form N-1

FIG. 15 shows the experimental and the simulated XRPD pattern of crystalline Compound (III), Form N-1, acquired at 25° C. using a spinning capillary sample. A list of the peaks are shown in Table 2, above. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-2.

II.4 Amorphous Compound (I)

FIG. 22 shows the experimental XRPD pattern of amorphous Compound (I) acquired at room temperature (about 25° C.). The spectra is characterized a broad peak and the absence of sharp peaks, which is consistent with an amorphous material.

III. Single Crystal X-Ray Study for Compound (III), Form N-1

Data were collected on a Bruker-Nonius CAD4 serial diffractometer. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Intensities were measured using Cu K α radiation ($\lambda=1.5418 \text{ \AA}$) at a constant temperature with the θ-2θ variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Alternately, single crystal data were collected on a Bruker-Nonius Kappa CCD 2000 system using Cu K α radiation ($\lambda=1.5418 \text{ \AA}$). Indexing and processing of the measured intensity data were carried out with the HKL2000 software package (Otwinowski, Z. & Minor, W. (1997) in Macromolecular Crystallography, eds. Carter, W. C. Jr & Sweet, R. M. (Academic, NY), Vol. 276, pp. 307-326) in the Collect program suite (Collect Data collection and processing user interface: Collect: Data collection software, R. Hooft, Nonius B. V., 1998). Alternately, single crystal data were collected on a Bruker-AXS APEX2 CCD system using Cu K α radiation ($\lambda=1.5418 \text{ \AA}$). Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27). When indicated, crystals were cooled in the cold stream of an Oxford cryo system (Oxford Cryosystems Cryostream cooler J. Cosier and A. M. Glazer, J. Appl. Cryst., 1986, 19, 105) during data collection.

The structures were solved by direct methods and refined on the basis of observed reflections using either the SDP software package (SDP, Structure Determination Package, Enraf-Nonius, Bohemia N.Y. 11716. Scattering factors, including f and f', in the SDP software were taken from the "International Tables for Crystallography", Kynoch Press, Birmingham, England, 1974; Vol IV, Tables 2.2A and 2.3.1) with minor local modifications or the crystallographic packages MAXUS (maXus solution and refinement software suite: S. Mackay, C. J. Gilmore, C. Edwards, M. Tremayne, N. Stewart, K. Shankland. maXus: a computer program for the solution and refinement of crystal structures from diffraction data) or SHELXTL (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27).

The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. The function minimized in the refinements was $\Sigma_w(|F_o| -$

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$|F_c|^2$. R is defined as $\Sigma|F_o|-|F_c|/\Sigma|F_o|$ while $R_w = [\Sigma_w(|F_o|-|F_c|)^2/\Sigma_w|F_o|^2]^{1/2}$ where w is an appropriate weighting function based on errors in the observed intensities. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors, but no hydrogen parameters were varied.

"Hybrid" simulated powder X-ray patterns were generated as described in the literature (Yin, S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougoutas, J. Z., *American Pharmaceutical Review*, 2003, 6, 2, 80). The room temperature cell parameters were obtained by performing a cell refinement using the CellRefine.xls program. Input to the program includes the 2-theta position of ca. 10 reflections, obtained from the experimental room temperature powder pattern; the corresponding Miller indices, hkl, were assigned based on the single-crystal data collected at low temperature. A new (hybrid) XRPD was calculated (by either of the software programs, Alex or LatticeView) by inserting the molecular structure determined at low temperature into the room temperature cell obtained in the first step of the procedure. The molecules are inserted in a manner that retains the size and shape of the molecule and the position of the molecules with respect to the cell origin, but, allows intermolecular distances to expand with the cell.

A single crystal, measuring 40x30x10 microns, was selected from the slurry of crystals described in Example 5 for single crystal diffraction analysis. The selected crystal was affixed to a thin glass fiber with a small amount of a light grease, and mounted at room temperature on a Brker ApexII single crystal diffractometer equipped with a rotating copper anode.

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Crystalline Compound (III), From N-1 is characterized by unit cell parameters approximately equal to those reported in Table 4. The unit cell parameters were measured at a temperature of about 25° C.

TABLE 4

a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°
Space group: P2 ₁ /n
Molecules of Compound (I)/unit cell: 4
Volume = 2969 Å ³

Structure solution and refinement were routine in the monoclinic space group, P2₁/n, with four formula units in the unit cell. The structure contains cations of N-(4-[{6,7-bis(methyloxy)-quinolin-4-yl}oxy]phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, protonated at the quinoline nitrogen atom, and singly ionized malic acid anions, in a 1:1 ratio. Further, the crystal contained a 1:1 ratio of (L)-malic acid ions to (D)-malic acid ions. Table 5 fractional atomic coordinates for Compound (III), Form N-1 calculated at a temperature of about 25° C.

Based on the single crystal X-ray data, crystalline Compound (III), Form N-1 may be characterized by a simulated powder x-ray diffraction (XRPD) pattern substantially in accordance with the simulated pattern shown in FIG. 15 and/or by an observed XRPD pattern substantially in accordance with the experimental pattern shown in FIG. 15.

TABLE 5

Fractional Atomic Coordinates for Compound (III), Form N-1 Calculated at a Temperature of about 25° C.							
Atom	X	Y	Z	Atom	X	Y	
O1	0.30601	-0.52166	0.22875	C40	0.25712	-0.35516	0.17574
O2	0.29518	0.12504	0.09391	C41	0.63543	0.13842	0.29041
O3	0.19041	-0.53232	0.18147	C42	0.22703	0.46640	0.06306
F5	-0.07307	2.12170	-0.08811	C43	0.34559	1.01717	-0.10021
O6	0.18186	1.20500	-0.03241	C44	0.39312	1.20834	-0.08137
O7	0.57137	0.22739	0.23473	C45	0.48224	0.32340	0.15059
O8	0.58700	-0.17911	0.24998	C46	0.77400	0.04784	0.34652
O9	0.41742	0.76377	-0.04319	C47	0.79349	0.09920	0.31966
N10	0.28649	0.82210	-0.01420	H10	0.22646	0.91057	-0.01479
O11	0.87391	0.22086	0.31241	H16	0.24790	1.42164	-0.10317
N12	0.46887	0.17029	0.17613	H19	-0.04176	1.82973	-0.03893
C13	0.29647	0.64886	0.01247	H20	0.16347	1.73025	-0.13083
C14	0.31416	1.08187	-0.06304	H22	0.43179	-0.17902	0.22447
C15	0.33900	-0.02207	0.14761	H23	0.17093	0.73524	0.03244
N16	0.20651	1.40640	-0.08267	H27	0.21953	-0.24212	0.12962
C17	0.40079	-0.01723	0.17602	H29	0.07954	1.50390	-0.03492
C18	0.29743	0.29956	0.06604	H30	0.04671	2.05817	-0.13354
C19	0.00418	1.80556	-0.05680	H33	0.41851	0.16255	0.04395
C20	0.11925	1.73626	-0.11097	H34	0.43433	0.41859	0.10106
C21	0.22556	1.24019	-0.05791	H38	0.41440	0.45648	-0.00227
C22	0.39150	-0.17467	0.20389	H41	0.61062	0.02238	0.31086
C23	0.22558	0.63870	0.03619	H42	0.17752	0.45794	0.07911
O24	0.62714	0.39565	0.29760	H45	0.53033	0.44239	0.15049
C25	0.34591	0.87438	-0.03961	H31a	0.76754	0.12071	0.26693
C26	0.36467	-0.51389	0.25773	H31b	0.74726	-0.15247	0.28137
C27	0.26562	-0.20277	0.14859	H43a	0.30237	1.06909	-0.12187
C28	0.35380	0.15272	0.12054	H43b	0.36868	0.85693	-0.10836
C29	0.07365	1.60604	-0.05443	H44a	0.45563	1.18725	-0.07495
C30	0.04897	1.92890	-0.11212	H44b	0.38932	1.39942	-0.08846
C31	0.73841	0.04517	0.28641	H26a	0.35958	-0.37184	0.27147
C32	0.32089	-0.35160	0.20385	H26b	0.42813	-0.55605	0.25348
C33	0.36641	0.29052	0.04302	H26c	0.34954	-0.66814	0.27571
C34	0.42458	0.32272	0.12143	H35a	0.08189	-0.39941	0.15398
C35	0.11723	-0.54030	0.15742	H35b	0.06671	-0.68838	0.16269
C36	0.12933	1.59042	-0.08228	H35c	0.13276	-0.61095	0.13323

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TABLE 5-continued

Fractional Atomic Coordinates for Compound (III), Form N-1 Calculated at a Temperature of about 25°C.							
Atom	X	Y	Z	Atom	X	Y	Z
C37	-0.00344	1.93494	-0.08547	H11	0.88836	0.21926	0.28968
C38	0.36439	0.47245	0.01586	H12	0.50720	0.16494	0.19477
C39	0.59040	0.05797	0.25625	H24	0.61522	0.45898	0.27789

IV. Solid State Nuclear Magnetic Resonance (SSNMR)

All solid-state C-13 NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and the TPPM pulse sequence and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A. E. Bennett et al, *J. Chem. Phys.*, 1995, 103, 6951), (G. Metz, X. Wu and S. O. Smith, *J. Magn. Reson. A*, 1994, 110, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance being set to 38.56 ppm (W. L. Earl and D. L. VanderHart, *J. Magn. Reson.*, 1982, 48, 35-54).

IV.1 Compound (I), Form N-1

The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-1 is shown in FIG. 2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

SS ^{13}C NMR Peaks: 18.1, 20.6, 26.0, 42.9, 44.5, 54.4, 55.4, 56.1, 70.4, 99.4, 100.1, 100.6, 114.4, 114.9, 115.8, 119.6, 120.1, 121.6, 123.2, 124.1, 136.4, 138.6, 140.6, 145.4, 150.1, 150.9, 156.2, 157.4, 159.4, 164.9, 167.1, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm.

FIG. 3 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

FIG. 4 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows a peak at -121.6, -120.8, and -118.0 ppm, ± 0.2 ppm.

IV.2 Compound (I), Form N-2

The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-2 is shown in FIG. 9. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

SS ^{13}C NMR Peaks: 20.5, 21.8, 23.0, 25.9, 26.4, 38.0, 41.7, 54.7, 55.8, 56.2, 56.6, 69.7, 99.4, 100.0, 100.4, 100.8, 102.3, 114.5, 115.5, 116.7, 119.0, 120.2, 121.1, 121.2, 122.1, 122.9, 124.5, 136.0, 137.3, 138.1, 138.9, 139.5, 140.2, 144.9, 145.7, 146.1, 150.7, 156.7, 157.5, 159.6, 159.7, 165.1, 167.0, 168.0, 171.5, 177.3, 179.3, 180.0, and 180.3 ppm, ± 0.2 ppm.

FIG. 10 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

FIG. 11 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at -121.0 and -119.1 ppm, ± 0.2 ppm. Those peaks, individually or together, may be sufficient to characterize crystalline Compound (I), Form N-2.

IV.3 Compound (III), Form N-1

The solid state ^{13}C NMR spectrum of crystalline Compound (III), Form N-1 is shown in FIG. 16. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

SS ^{13}C NMR Peaks: 20.8, 26.2, 44.8, 55.7, 70.7, 1M.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, and 182.1 ppm, ± 0.2 ppm.

FIG. 17 shows the solid state ^{15}N NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows peaks at 119.6, 134.7, and 175.5 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

FIG. 18 shows the solid state ^{19}F NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows a peak at -120.5 ppm, 10.2 ppm.

IV.4 Compound (I), Amorphous

FIG. 23 shows the solid state ^{13}C NMR spectrum of amorphous Compound (I). The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

SS ^{13}C NMR Peaks (ppm): 12.2, 17.8, 20.3, 21.8, 27.2, 33.8, 41.7, 56.9, 69.9, 99.9, 102.2, 115.6, 122.2, 134.4, 137.8, 142.9, 149.1, 150.9, 157.3, 159.7, 167.0, 171.7, 173.1, 177.4, and 179.5 ppm, ± 0.2 ppm.

FIG. 24 shows the solid state ^{15}N NMR spectrum of amorphous Compound (I). The spectrum shows peaks at 120.8, 131.8, 174.7, and 178.3 ppm, 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

FIG. 25 shows the solid state ^{19}F NMR spectrum of amorphous Compound (I). The spectrum shows a peak at -118.9 ppm, ± 0.2 ppm.

V. Thermal Characterization Measurements**Thermal Gravimetric Analysis (TGA)**

The TGA measurements were performed in a TA Instruments™ model Q500 or 2950, employing an open pan setup. The sample (about 10-30 mg) was placed in a platinum pan previously tared. The weight of the sample was measured accurately and recorded to a thousand of a milligram by the instrument. The furnace was purged with nitrogen gas at 100 mL/min. Data were collected between room temperature and 300° C. at 10° C./min heating rate.

Differential Scanning Calorimetry (DSC) Analysis

DSC measurements were performed in a TA Instruments™ model Q2000, Q1000 or 2920, employing an open pan setup. The sample (about 2-6 mg) was weighed in an aluminum pan and recorded accurately to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50 mL/min. Data were collected between room temperature and 300° C. at 10° C./min heating rate. The plot was made with the endothermic peaks pointing down.

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31**V.1 Compound (I), Form N-1**

FIG. 5 shows the TGA thermogram for crystalline Compound (I), Form N-1, which shows a weight loss of approximately 0.4 weight % at a temperature of 170° C.

FIG. 6 shows the DSC thermogram for crystalline Compound (I), Form N-1, which showed a melting point of approximately 187° C.

V.2 Compound (I), Form N-2

FIG. 12 shows the TGA thermogram for crystalline Compound (I), Form N-2, which shows a weight loss of approximately 0.1 weight % at a temperature of 170° C.

FIG. 13 shows the DSC thermogram for crystalline Compound (I), Form N-2, which showed a melting point of approximately 186° C.

V.3 Compound (III), Form N-1

FIG. 19 shows the TGA thermogram for crystalline Compound (III), Form N-1, which shows a weight loss of approximately 0.2 weight % at a temperature of 170° C.

FIG. 20 shows the DSC thermogram for crystalline Compound (III), Form N-1, which showed a melting point of approximately 186° C.

V.2 Compound (I), Amorphous

FIG. 26 shows the DSC for crystalline Compound (I).

VI. Moisture Vapor Isotherm Measurements

Moisture sorption isotherms were collected in a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was dried at 60° C. until the loss rate of 0.0005 wt %/min was obtained for 10 minutes. The sample was tested at 25° C. and 3 or 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95% RH. Equilibration at each RH was reached when the rate of 0.0003 wt %/min for 35 minutes was achieved or a maximum of 600 minutes.

VI.1 Compound (I), Form N-1

FIG. 7 shows the moisture vapor isotherm of crystalline Compound (I), Form N-1.

VI.2 Compound (I), Form N-1

FIG. 14 shows the moisture vapor isotherm of crystalline Compound (I), Form N-2.

VI.3 Compound (III), Form N-1

FIG. 21 shows the moisture vapor isotherm of crystalline Compound (III), Form N-1.

32**VI.4 Compound (I), Amorphous**

FIG. 27 shows the moisture vapor isotherm of amorphous Compound (I).

The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. N-(4-[{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is crystalline.

2. The N-(4-[{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is the (DL)-malate salt.

3. The N-(4-[{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is the (L)-malate salt or (D)-malate salt.

4. The N-(4-[{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (L)-malate salt.

5. The N-(4-[{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (D)-malate salt.

* * * * *



JOINT EXHIBIT

JTX-0002

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Appx142



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(12) United States Patent
Brown et al.

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(45) Date of Patent: *Aug. 17, 2021

- (54) **MALATE SALT OF N-(4-{[6,7-BIS(METHYLOXY)QUINOLIN-4-YL]OXY}PHENYL)-N'-(4-FLUOROPHENYL)CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEREOF FOR THE TREATMENT OF CANCER**
- (71) Applicant: Exelixis, Inc., Alameda, CA (US)
- (72) Inventors: Adrian St. Clair Brown, Ely (GB); Peter Lamb, Oakland, CA (US); William P. Gallagher, Princeton, NJ (US)
- (73) Assignee: Exelixis, Inc., Alameda, CA (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
This patent is subject to a terminal disclaimer.
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Primary Examiner — Timothy R Rozof*(74) Attorney, Agent, or Firm* — Honigman LLP; Heidi M. Berven**(57) ABSTRACT**

Disclosed are malate salts of N-(4-[{6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including a (L)-malate salt, a (D)-malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salt of N-(4-[{6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-[{6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

3 Claims, 27 Drawing Sheets**(56) References Cited****U.S. PATENT DOCUMENTS**

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Appx147

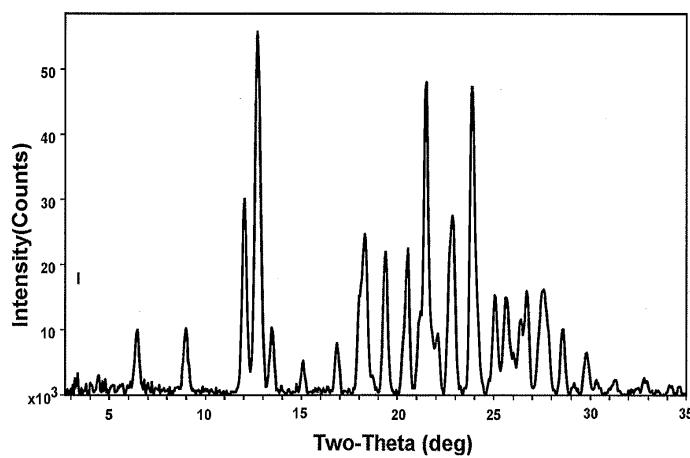
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Figure 1



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Appx148

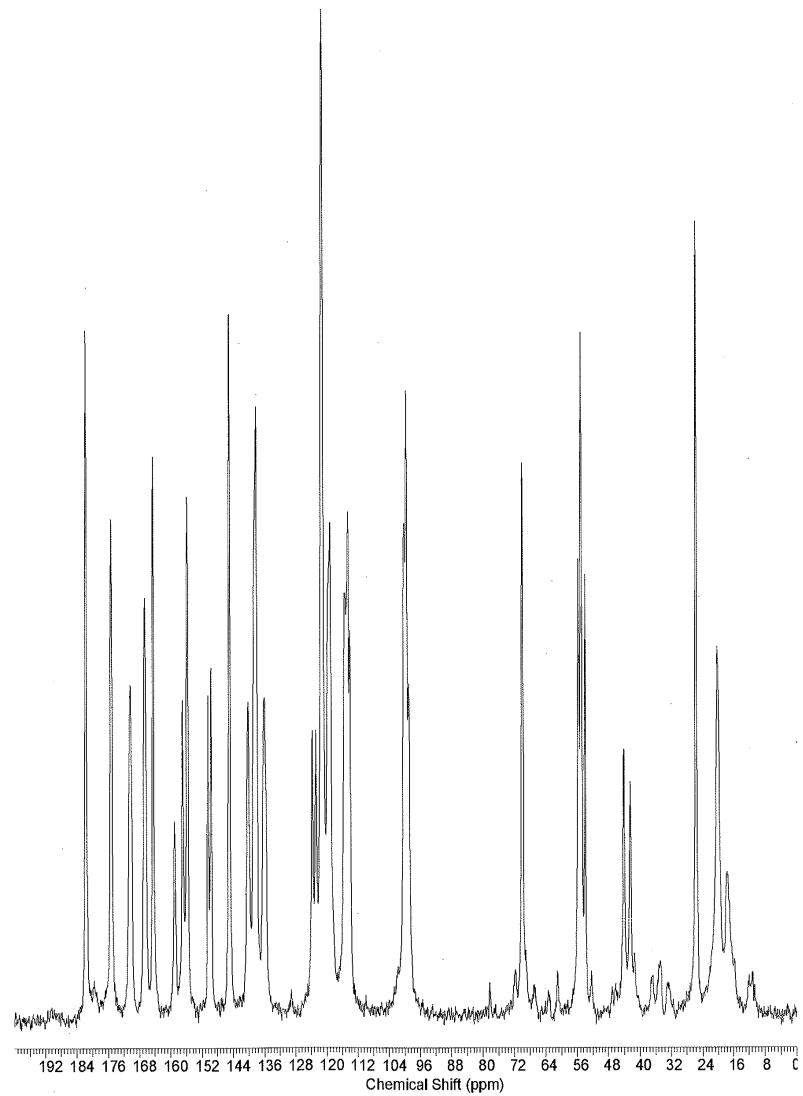
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Figure 2



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Appx149

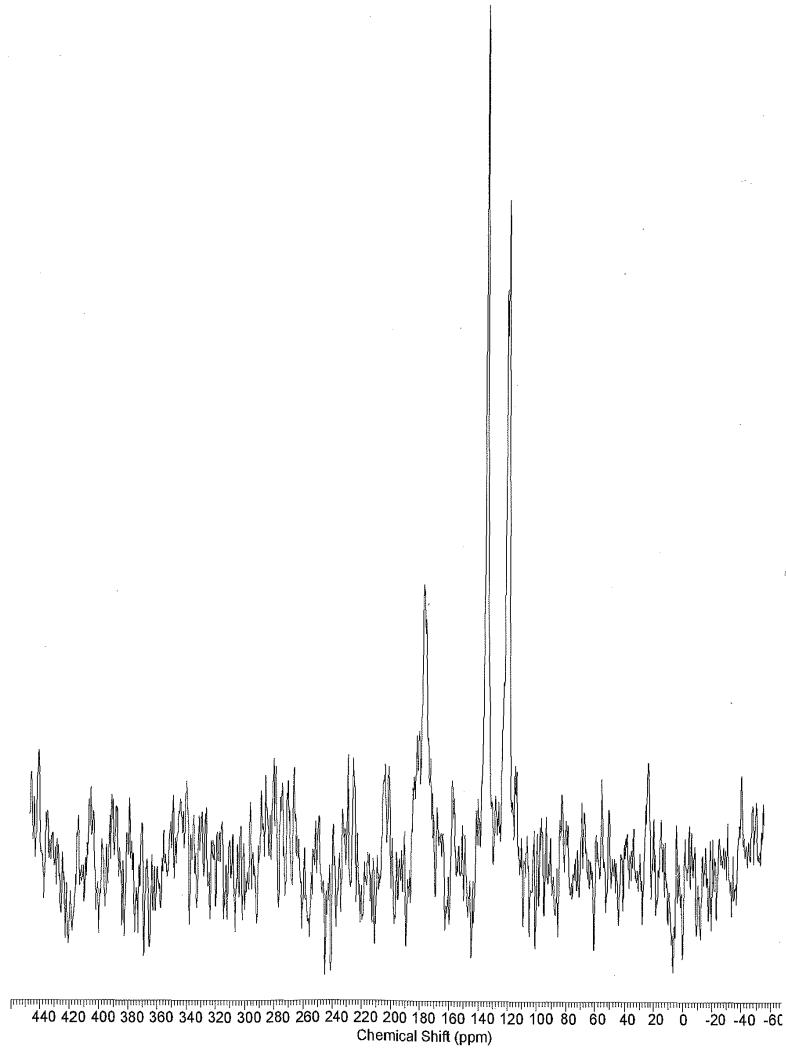
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Figure 3



EXEL2_00132237

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Appx150

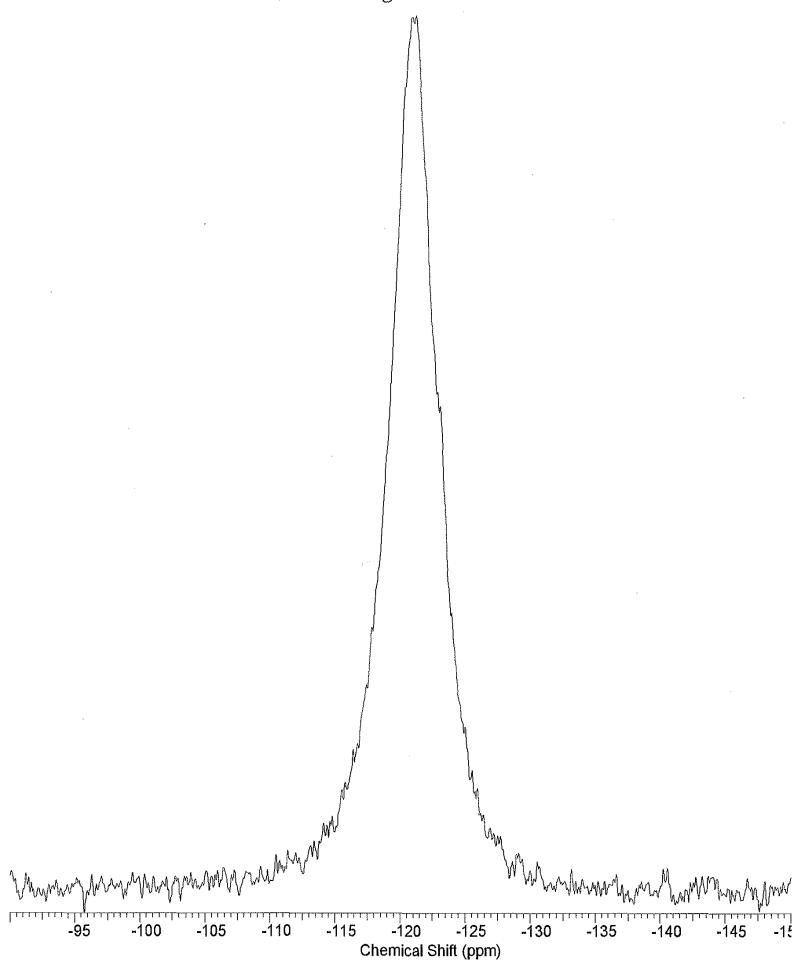
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Figure 4



EXEL2_00132238

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Appx151

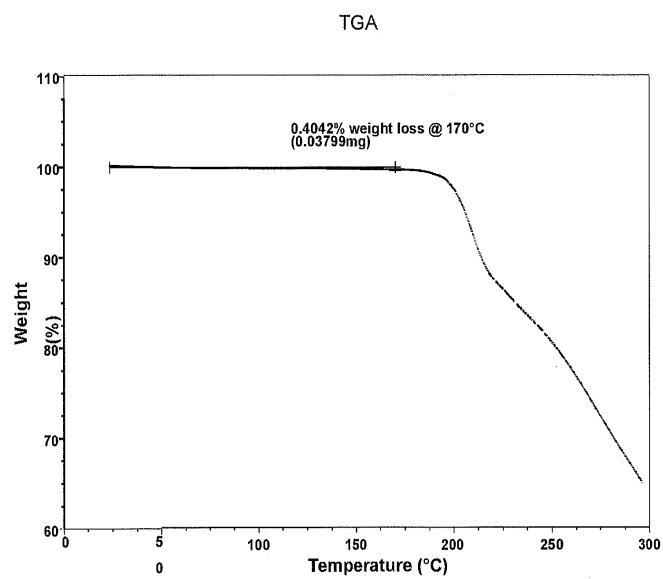
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Figure 5



EXEL2_00132239

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Appx152

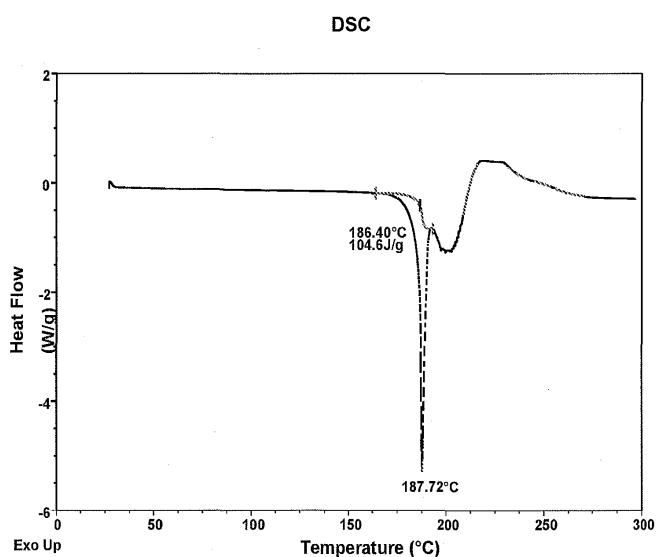
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Figure 6



EXEL2_00132240

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Appx153

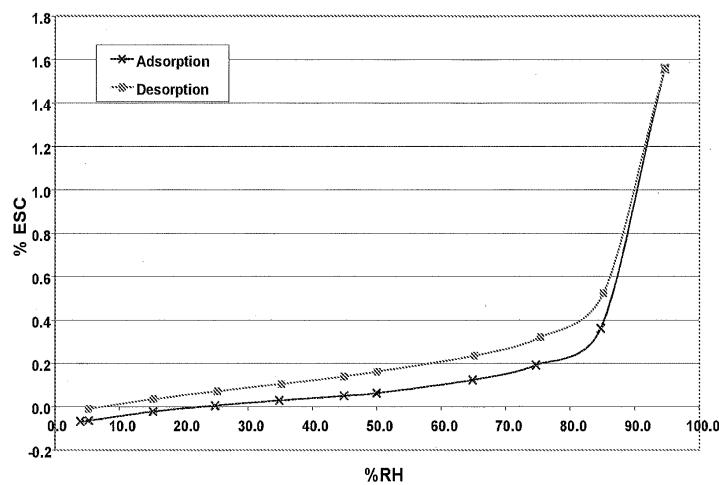
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Figure 7



Moisture Sorption of Compound (I), Form N-1

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Appx154

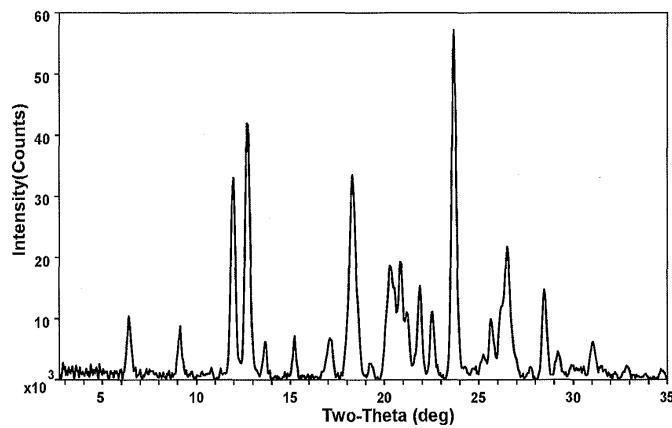
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Figure 8



EXEL2_00132242

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Appx155

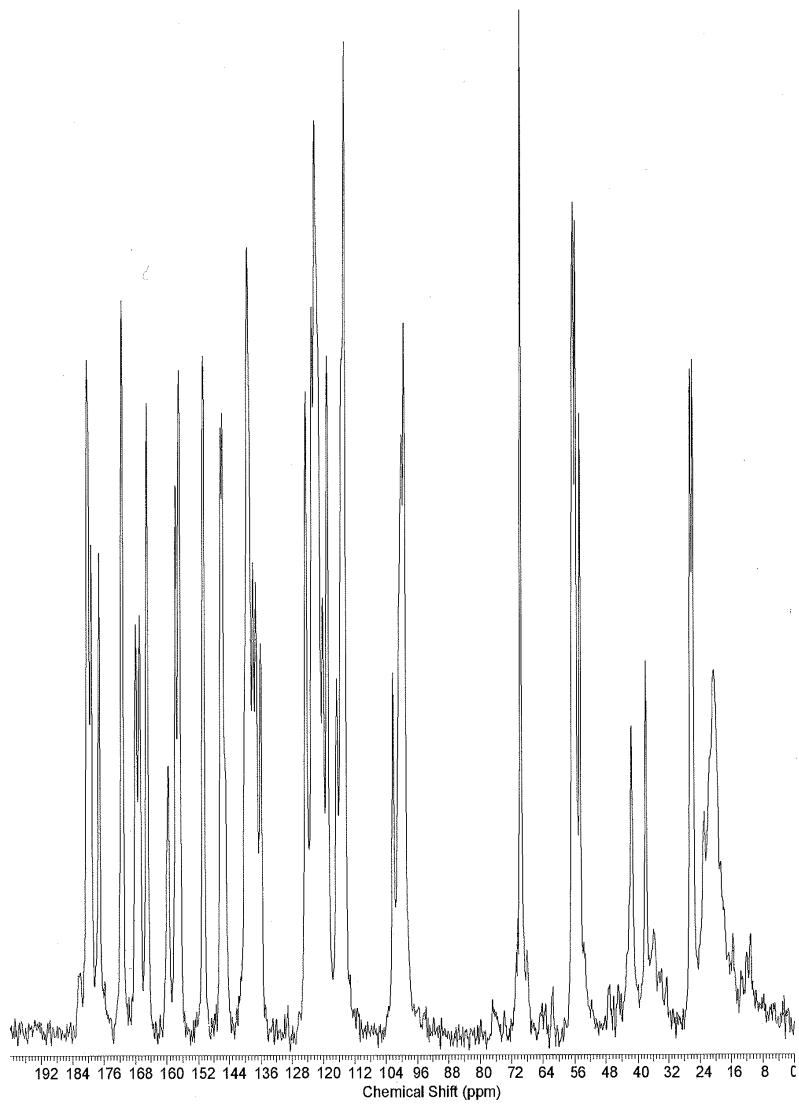
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Figure 9



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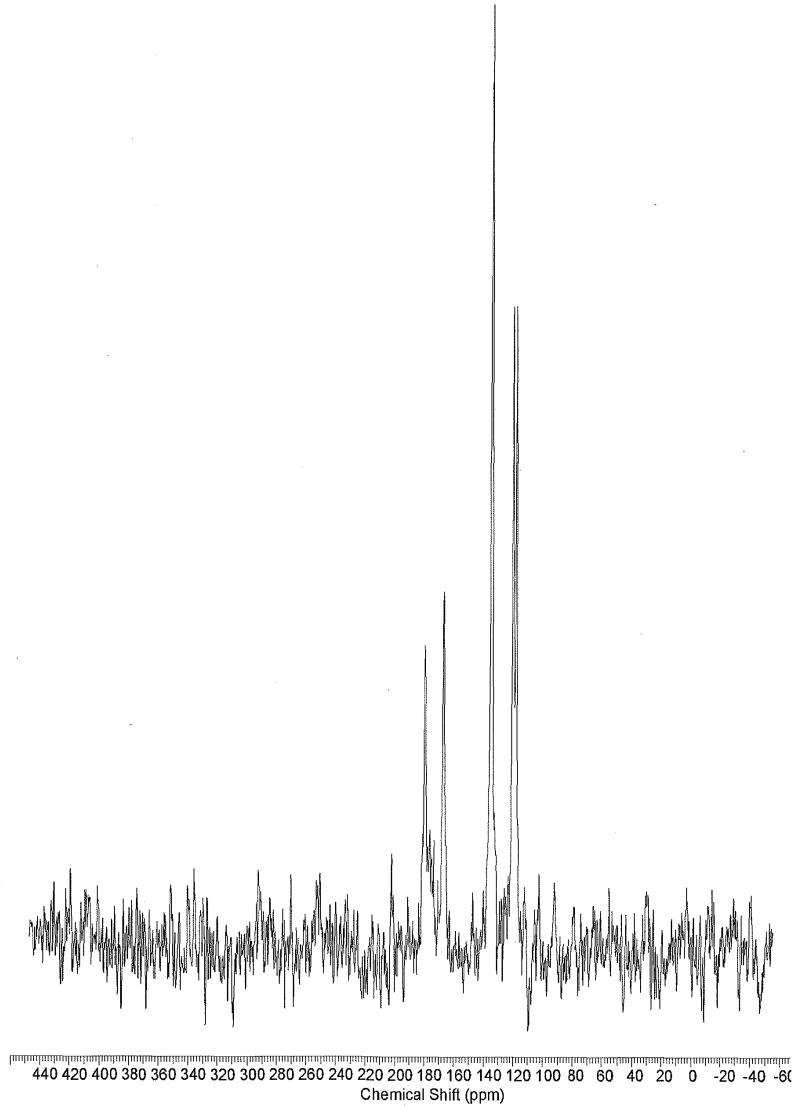
Appx156

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Figure 10



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Appx157

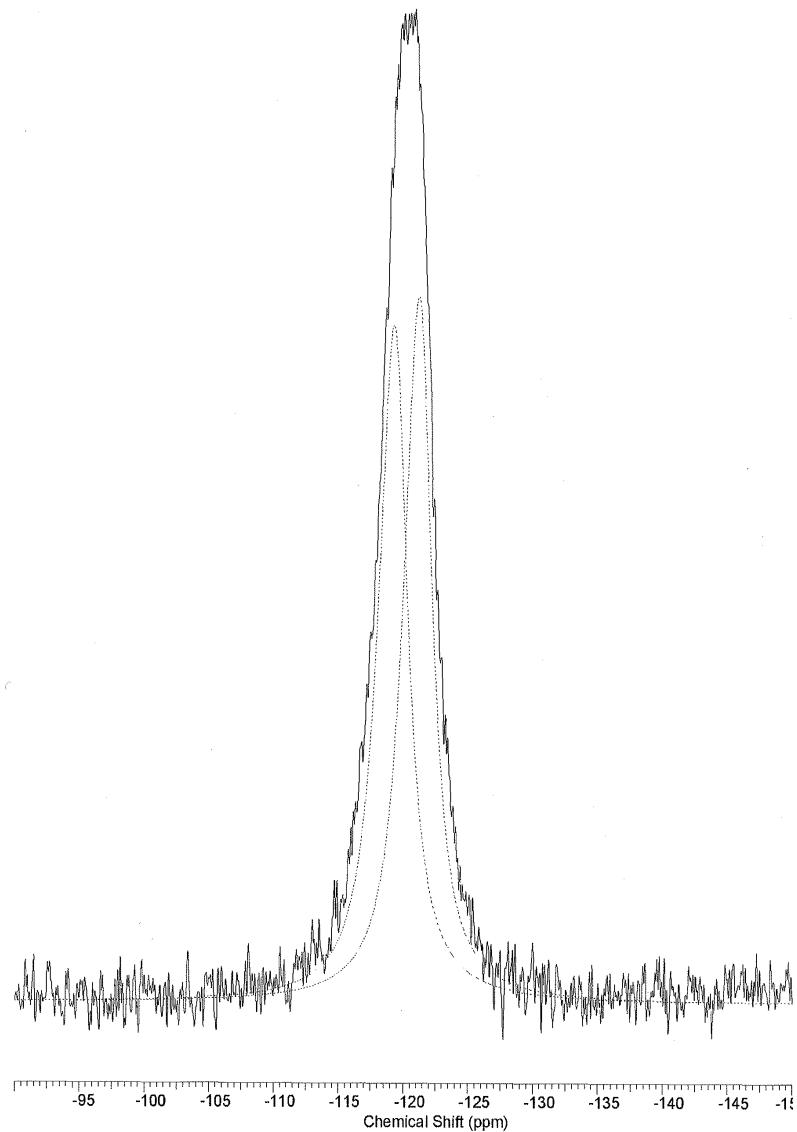
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Figure 11



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Appx158

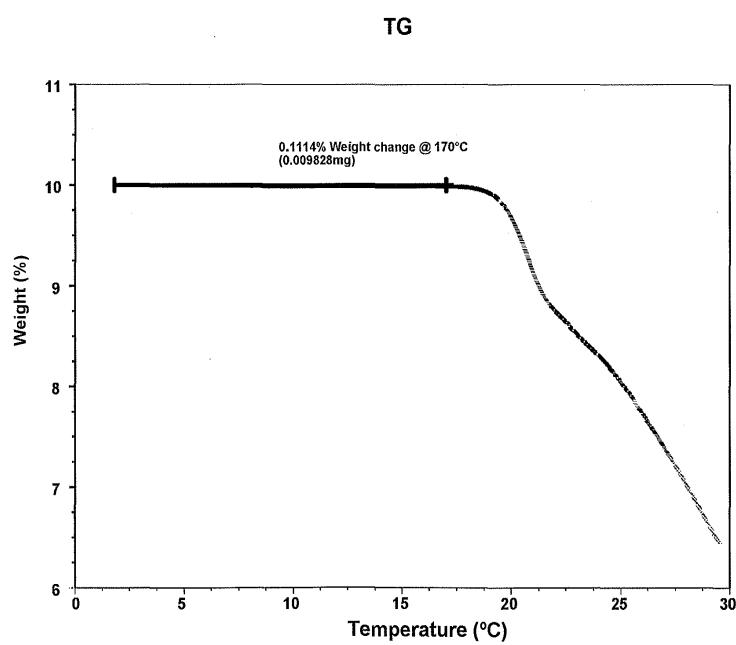
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Figure 12



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Appx159

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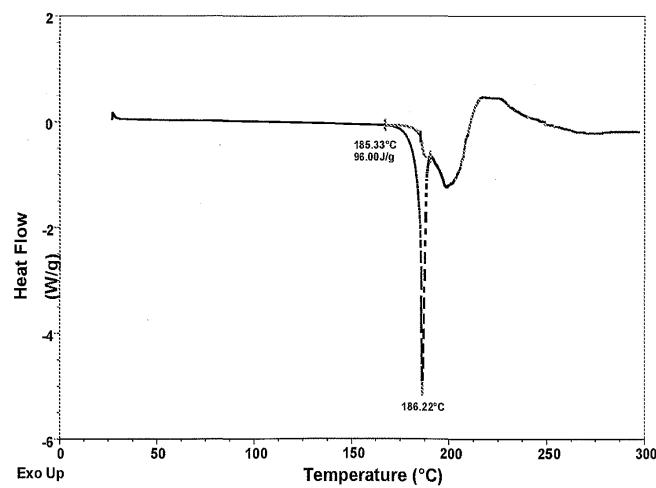
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Figure 13

DSC



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Appx160

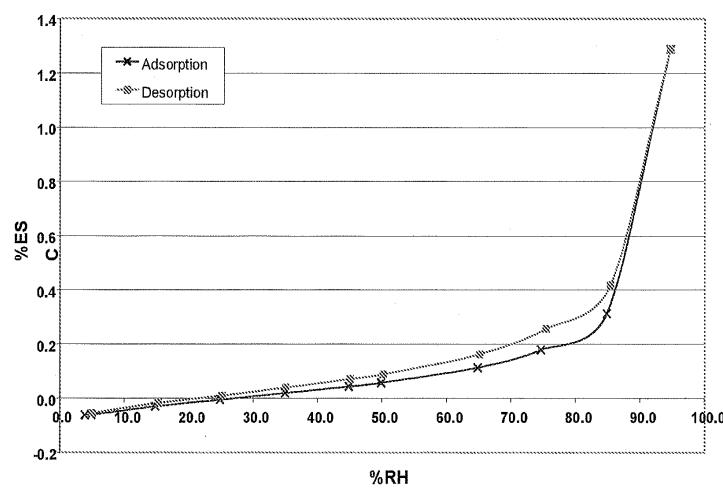
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Figure 14



EXEL2_00132248

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Appx161

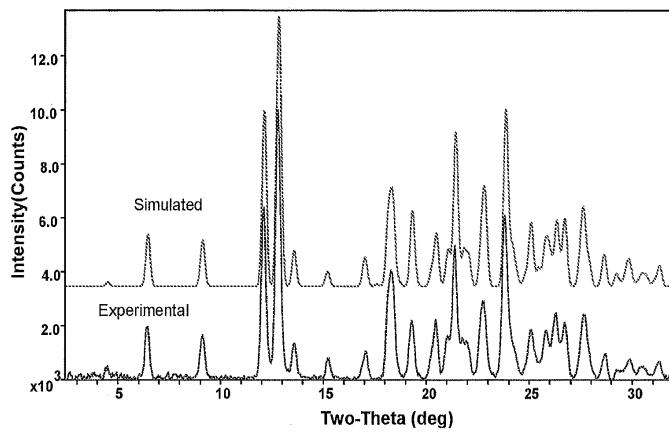
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Figure 15



EXEL2_00132249

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Appx162

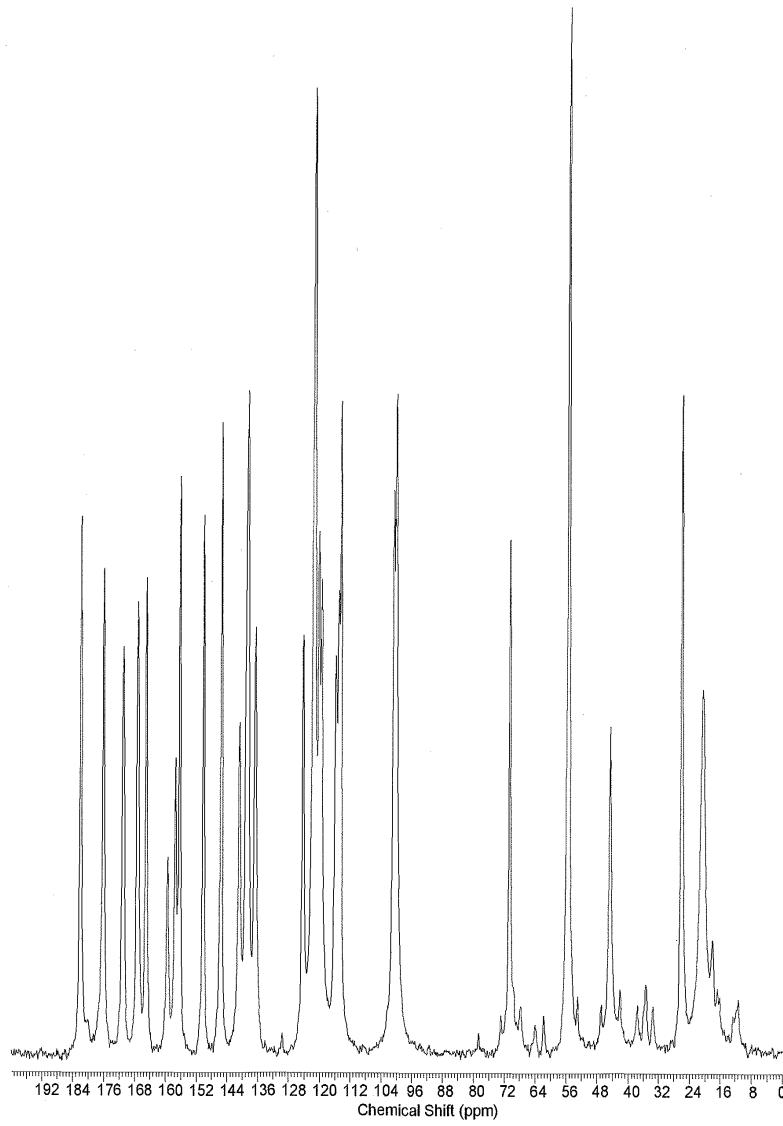
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Figure 16



EXEL2_00132250

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Appx163

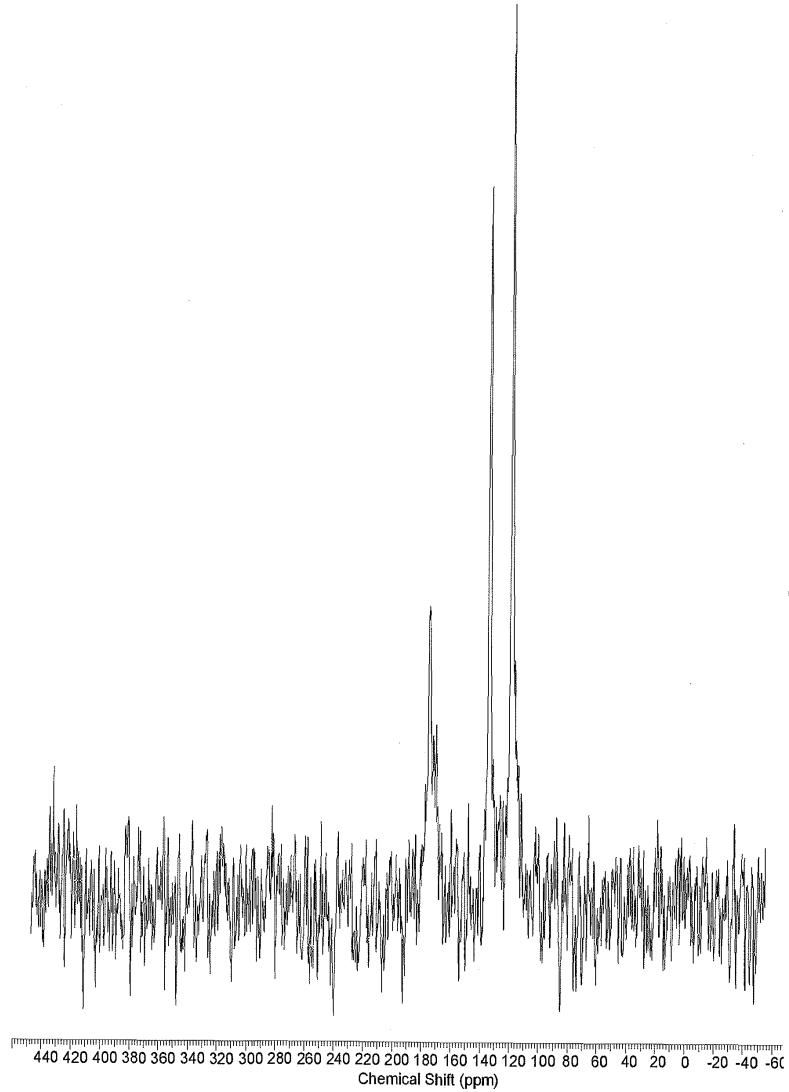
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Figure 17



EXEL2_00132251

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Appx164

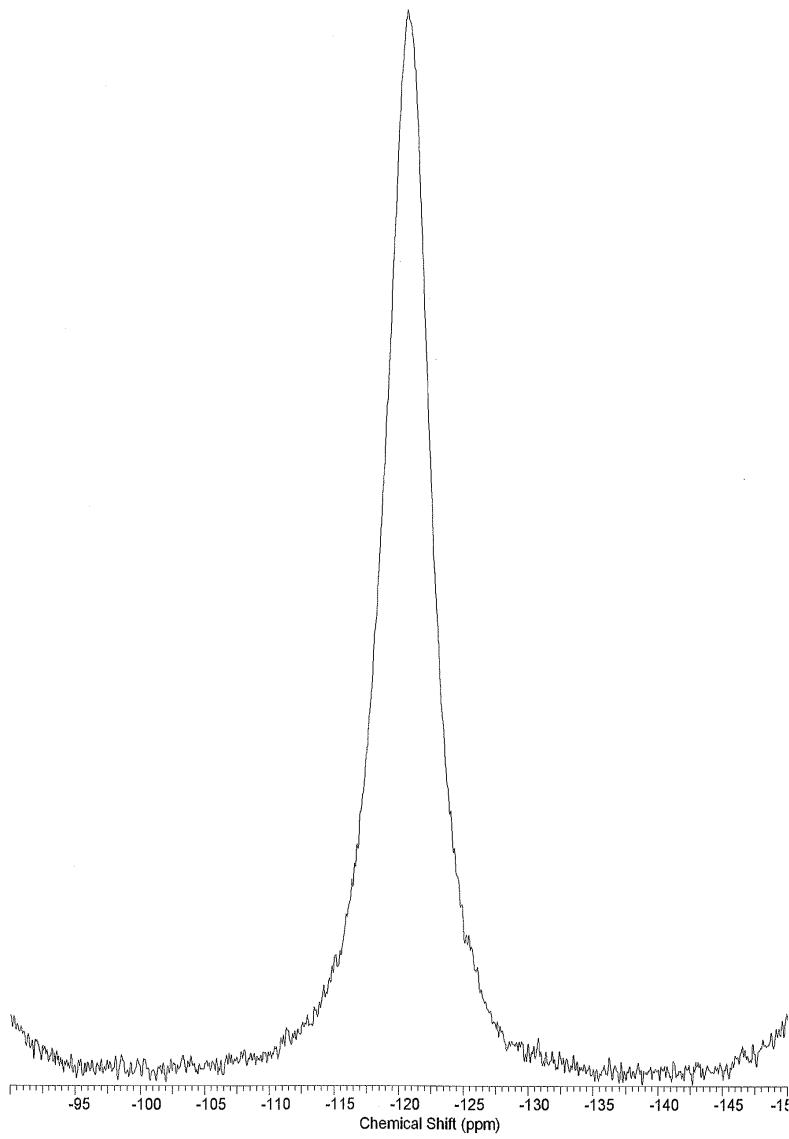
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Figure 18



EXEL2_00132252

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Appx165

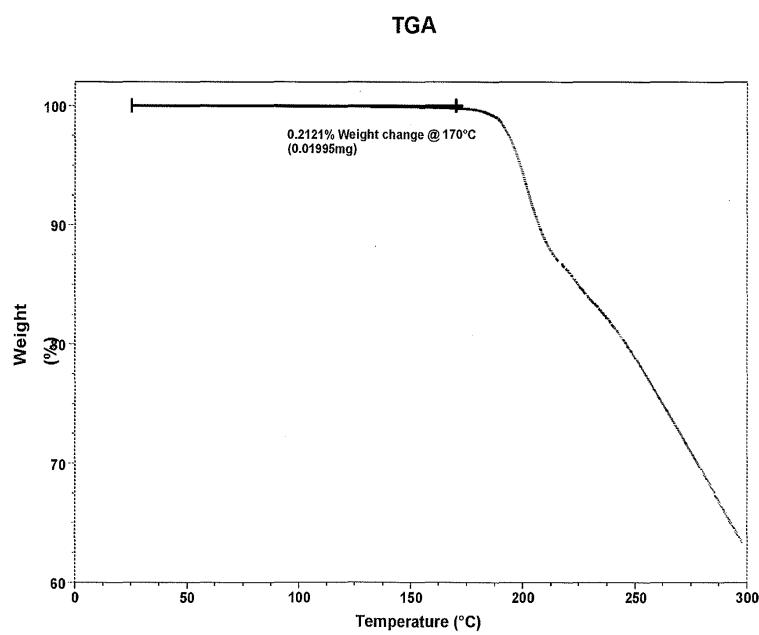
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Figure 19



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Appx166

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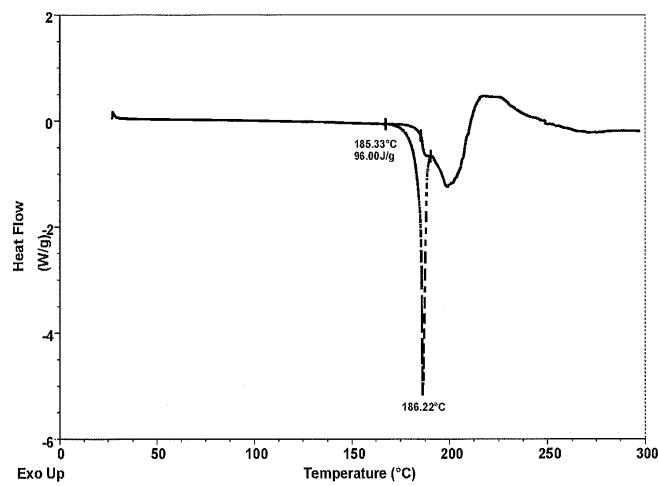
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Figure 20

DSC



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Appx167

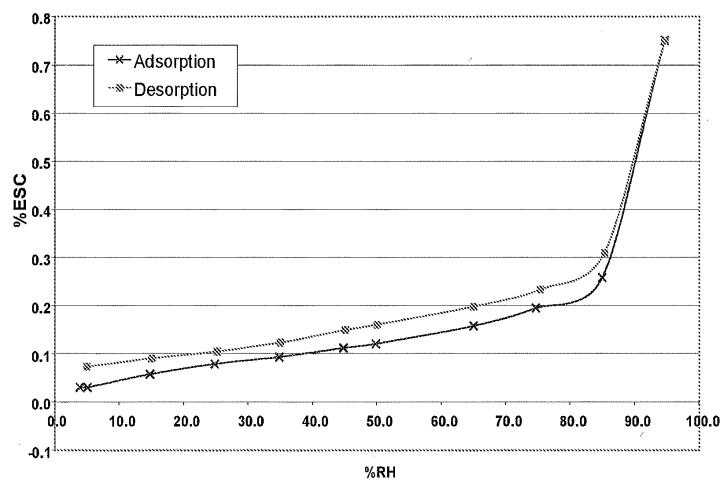
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Figure 21



EXEL2_00132255

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Appx168

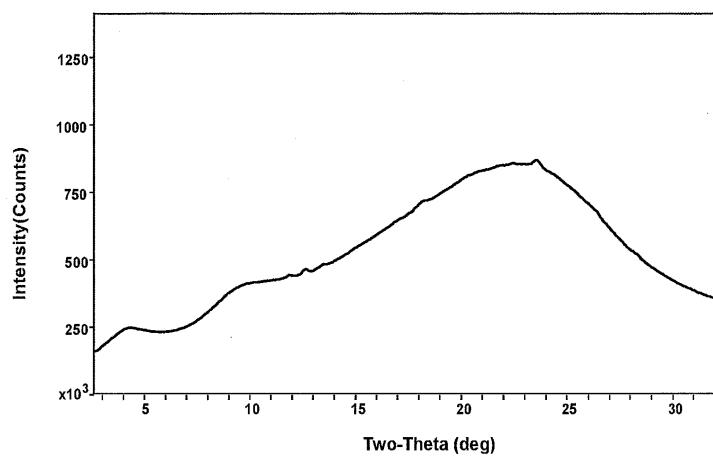
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Figure 22



EXEL2_00132256

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Appx169

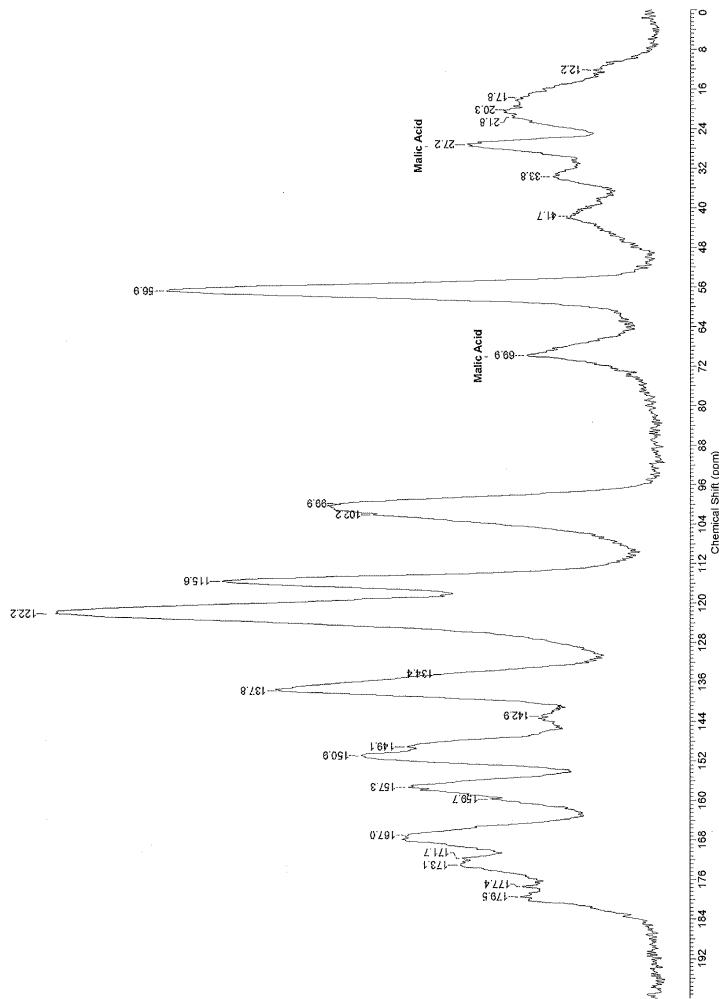
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Figure 23



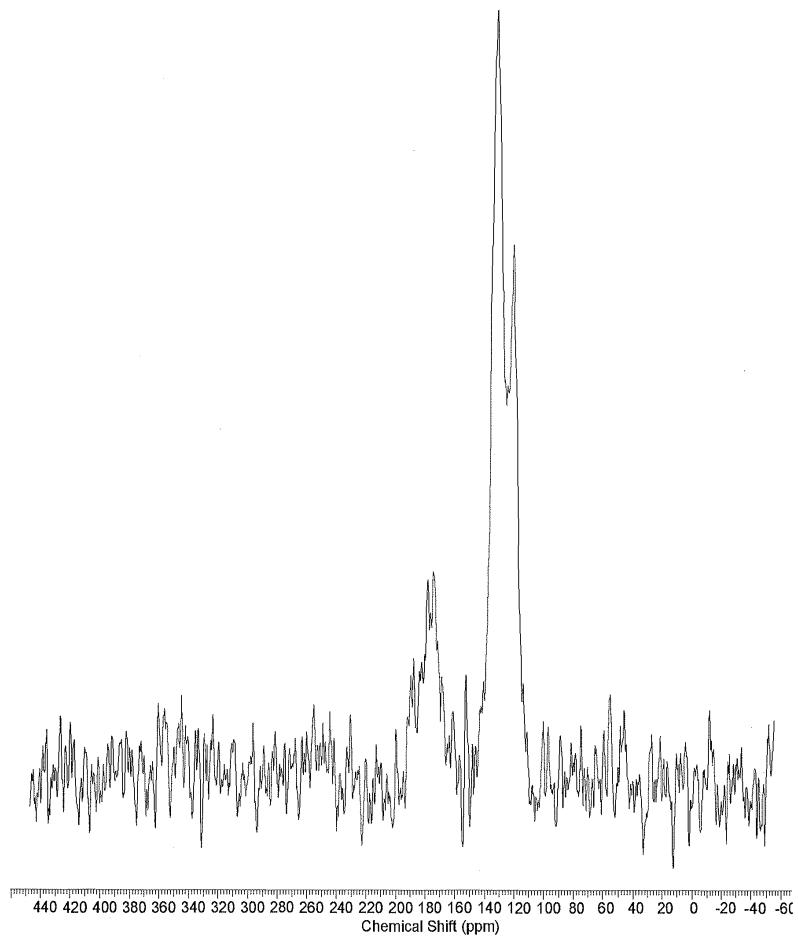
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Figure 24



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Appx171

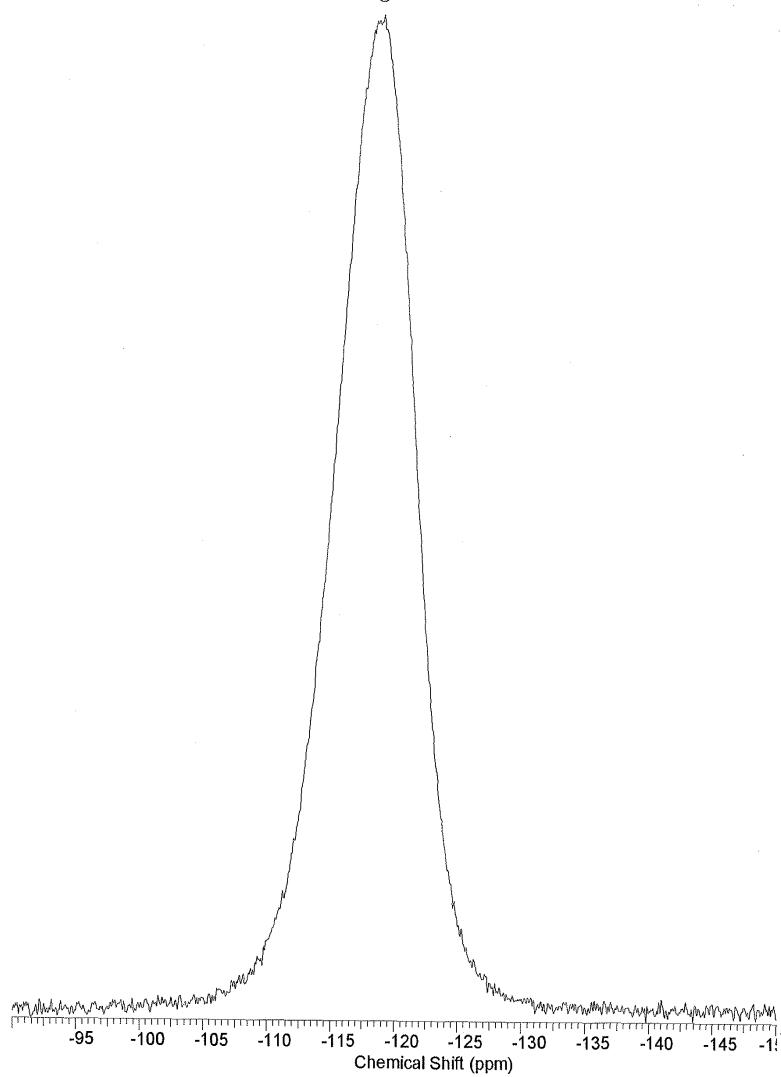
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Figure 25



EXEL2_00132259

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Appx172

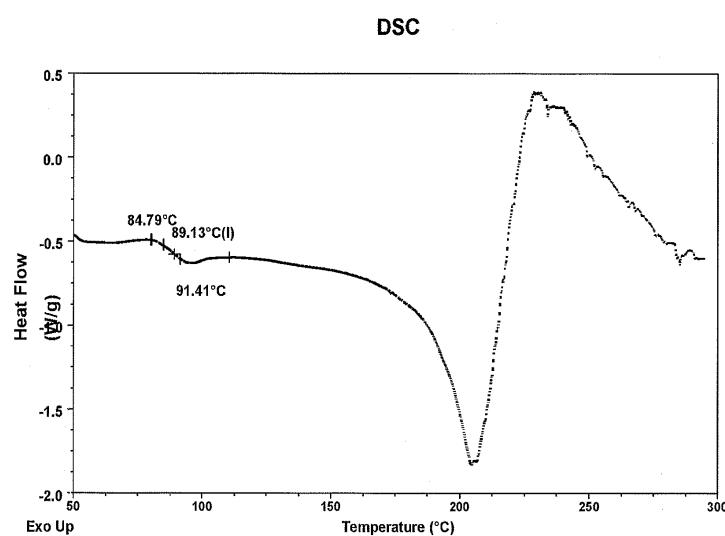
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Figure 26



EXEL2_00132260

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Appx173

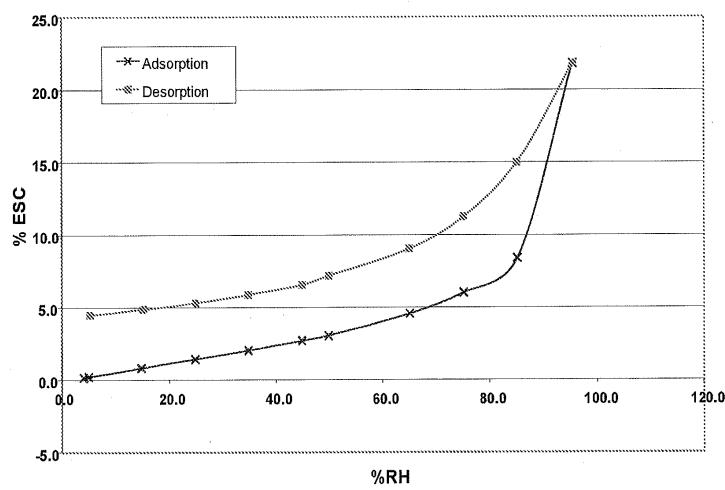
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Figure 27



EXEL2_00132261

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Appx174

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**MALATE SALT OF
N-(4-{[6,7-BIS(METHOXY)
QUINOLIN-4-YLOXY}PHENYL)-
N'(4-FLUOROPHENYL)CYCLOPROPANE-1,1
-DICARBOXAMIDE, AND CRYSTALLINE
FORMS THEREOF FOR THE TREATMENT
OF CANCER**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation application of U.S. Ser. No. 17/070,514, filed Oct. 14, 2020, which is a continuation application of U.S. Ser. No. 16/796,250, filed Feb. 20, 2020, which is a continuation application of U.S. Ser. No. 15/617,725, filed Jun. 8, 2017, which is a division of U.S. Ser. No. 14/340,871, filed Jul. 25, 2014, which is a division of U.S. Ser. No. 13/145,054, filed Oct. 20, 2011, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2010/021194, filed Jan. 15, 2010, which claims the benefit of U.S. provisional application No. 61/145,421, filed Jan. 16, 2009, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to malate salts of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{4-fluorophenyl)cyclopropane-1,1-dicarboxamide and to crystalline and amorphous forms of the malate salts of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{4-fluorophenyl)cyclopropane-1,1-dicarboxamide. The malate salts of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{4-fluorophenyl)cyclopropane-1,1-dicarboxamide include one of (1) the (L)-malate salt, (2) the (D)-malate salt, (3) the (D,L)-malate salt, and (4) mixtures thereof. The disclosure also relates to pharmaceutical compositions comprising at least one malate salt of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure also relates to pharmaceutical compositions comprising a crystalline or an amorphous form of at least one malate salt of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure also relates to methods of treating cancer comprising administering at least one malate salt of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure further relates to methods of treating cancer comprising administering a crystalline or an amorphous form of at least one malate salt of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

BACKGROUND

Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example,

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thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., *DN&P* 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery.

Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis in vivo (See: Maulik et al *Cytokine & Growth Factor Reviews* 2002 13, 41-59). c-Met, VEGFR2 and/or Ret overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components). The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and convert it into an oncogene product.

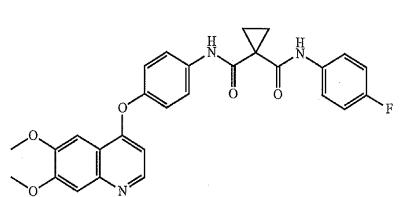
Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc. Technol.* 20016, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both vascular endothelial growth factor (VEGF) receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc. Technol.* 20016, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition.

Accordingly, small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including Ret, c-Met and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{4-fluorophenyl)cyclopropane-1,1-dicarboxamide, which has the chemical structure:

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WO 2005/030140 describes the synthesis of N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Example 12, 37, 38, and 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289). Example 48 is on paragraph [0353] in WO 2005/030140.

Besides therapeutic efficacy, the drug developer endeavors to provide a suitable form of the therapeutic agent that has properties relating to processing, manufacturing, storage stability, and/or usefulness as a drug. Accordingly, the discovery of a form that possesses some or all of these desired properties is vital to drug development.

Applicants have found a salt form of the drug N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide that has suitable properties for use in a pharmaceutical composition for the treatment of a proliferative disease such as cancer. The novel salt form of the invention exists in crystalline and amorphous forms

SUMMARY

This disclosure relates to malate salts of N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

Another aspect relates to crystalline and amorphous forms of the malate salts of N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the experimental XRPD pattern for crystalline Compound (I), Form N-1 at 25° C.

FIG. 2 shows the solid state ¹³C NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 3 shows the solid state ¹⁵N NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 4 shows the solid state ¹⁹F NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 5 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-1.

FIG. 6 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-1.

FIG. 7 shows the moisture sorption of crystalline Compound (I), Form N-1.

FIG. 8 shows the experimental XRPD pattern for crystalline Compound (I), Form N-2 at 25° C.

FIG. 9 shows the solid state ¹³C NMR spectrum of crystalline Compound (I), Form N-2.

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FIG. 10 shows the solid state ¹⁵N NMR spectrum of crystalline Compound (I), Form N-2.

FIG. 11 shows the solid state ¹⁹F NMR spectrum of crystalline Compound (I), Form N-2.

FIG. 12 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-2.

FIG. 13 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-2.

FIG. 14 shows the moisture sorption of crystalline Compound (I), Form N-2.

FIG. 15 shows the experimental and simulated XRPD patterns for crystalline Compound (III), Form N-1 at room temperature.

FIG. 16 shows the solid state ¹³C NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 17 shows the solid state ¹⁵N NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 18 shows the solid state ¹⁹F NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 19 shows the thermal gravimetric analysis (TGA) of crystalline Compound (III), Form N-1.

FIG. 20 shows the differential scanning calorimetry (DSC) of crystalline Compound (III), Form N-1.

FIG. 21 shows the moisture sorption of crystalline Compound (III), Form N-1.

FIG. 22 shows the XRPD pattern of amorphous Compound (I) at room temperature.

FIG. 23 shows the solid state ¹³C NMR spectrum of amorphous Compound (I).

FIG. 24 shows the solid state ¹⁵N NMR spectrum of amorphous Compound (I).

FIG. 25 shows the solid state ¹⁹F NMR spectrum of amorphous Compound (I).

FIG. 26 shows the differential scanning calorimetry (DSC) of amorphous Compound (I).

FIG. 27 shows the moisture sorption of amorphous Compound (I).

DETAILED DESCRIPTION

This disclosure relates to improvements of the physicochemical properties of N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, whereby this compound may be suitable for drug development. Disclosed herein are malate salts of N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. New solid state forms of those salts are also disclosed. The malate salts as well as their crystalline and amorphous forms disclosed herein each represent separate aspects of the disclosure. Although the malate salts and their solid state forms are described herein, the invention also relates to novel compositions containing the disclosed salts and solid state forms. Therapeutic uses of the salts and solid state forms described as well as therapeutic compositions containing them represent separate aspects of the disclosure. The techniques used to characterize the salts and their solid state forms are described in the examples below. These techniques, alone or in combination, may be used to characterize the salts and their solid state forms disclosed herein. The salts and their solid state forms may be also characterized by reference to the disclosed figures.

N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was found to have an enzyme Ret IC₅₀ value of about 5.2 nM (nanomolar) and an enzyme c-Met IC₅₀ value of about 1.3

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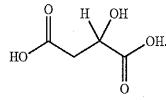
nM (nanomolar). The assay that was used to measure this c-Met activity is described in paragraph [0458] in WO2005-030140.

RET biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described in WO2005-030140. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 2 μM ATP, 1 μM poly-EY and 15 nM RET (baculovirus expressed human RET kinase domain M700-D1042 with a (His)₆ tag on the N-terminus) in a 20 uL assay buffer (20 mM Tris-HCl pH 7.5, 10 mM MgCl₂, 0.01% Triton X-100, 1 mM DTT, 3 mM MnCl₂). The mixture was incubated at ambient temperature for 2 hours after which 20 uL luciferase-luciferin mix was added and the chemiluminescent signal read using a Wallac Victor² reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5 ug/mL oxalic acid (pH 7.8), 5 mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μM AMP, 28 μg/ml luciferin and 40,000 units of light/mL luciferase.

Malate Salts of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide

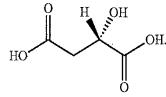
This disclosure relates to malate salts of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide. These malate salts are a combination of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide with malic acid which forms a 1:1 malate salt of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Malic acid has the following structure:



Due to its chiral carbon, two enantiomers of malic acid exist, (L)-malic acid and (D)-malic acid.

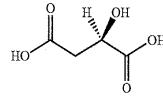
(L)-malic acid has the following structure:



There are various names or designations for the (L)-malic acid that are known in the art. These include butanedioic acid, hydroxy-, (2S)-(9CI); butanedioic acid, hydroxy-, (S)-; malic acid, L-(8CI); malic acid, 1-(3CI); (-)(S)-malic acid; (-)-Hydroxysuccinic acid; (-)(L)-malic acid; (-)-malic acid; (2S)-2-hydroxybutanedioic acid; (2S)-2-hydroxysuccinic acid; (S)-malic acid; apple acid; L(-)-malic acid; (L)-malic acid; NSC 9232; S(-)-malic acid; and S-2-hydroxybutanedioic acid.

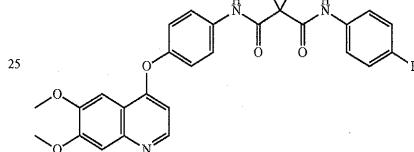
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(D) malic acid has the following structure:



10 There are various names or designations for the (D)-malic acid that are known in the art. These include butanedioic acid, 2-hydroxy-, (2R); butanedioic acid, hydroxy-, (2R)-(9CI); butanedioic acid, hydroxy-, (R)-; (+)-malic acid; (2R)-2-hydroxybutanedioic acid; (2R)-malic acid; (R)(+)-malic acid; (R)-malic acid; D-(+)-2-hydroxysuccinic acid; D-(+)-malic acid; and D-malic acid.

As discussed above, the chemical structure of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide is



30 There are no chiral carbons in its chemical structure. There are various names for N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide which are publicly known, and some of these various names or designations include 1,1-cyclopropanedicarboxamide, N-[4-[{6,7-dimethoxy-4-quinolinyloxy]phenyl]-N'-({4-fluorophenyl)-N-oxide, and 1,1-cyclopropanedicarboxamide, N-[4-[{6,7-dimethoxy-4-quinolinyloxy]phenyl]-N'-({4-fluorophenyl)-(9CI).

40 N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide can be prepared according to any of several different methodologies, either on a gram scale (<1 kg) or a kilogram scale (>1 kg). A gram-scale method is set forth in WO 2005-030140, 45 which describes the synthesis of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Examples 25, 37, 38, and 48), which is hereby incorporated by reference. Alternatively, N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including the active compound(s), can be prepared on a kilogram scale using the procedure set forth in Example 1 below.

45 This disclosure relates to malate salts of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide:

the (L)-malate salt of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide; (Compound I);

the (D)-malate salt of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound II); and

the (DL)-malate salt of N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Compound III).

55 Each has improved properties over N-(4-[{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl]-N'-({4-fluorophenyl)cyclopropane-1,1-dicarboxamide and its other salts. The names

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used herein to characterize a specific form, e.g. "N-2" etc., are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics, but rather such names are used as mere identifiers that are to be interpreted in accordance with the characterization information presented herein.

The malate salts of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-4-fluorophenyl)cyclopropane-1,1-dicarboxamide, and particularly Compound (I), have a preferred combination of pharmaceutical properties for development. Under the conditions of 25° C./60% relative humidity (RH) and 40° C./60% RH, Compound (I) showed no change in assay, purity, moisture and dissolution. The DSC/TGA showed the Compound (I) to be stable up to 185° C. No solvent losses were observed. The uptake of water by the (L)-malate salt was reversible with a slight hysteresis. The amount of water taken up was calculated at about 0.60 wt % at 90% RH. The (L)-malate salt was synthesized with good yield and purity >90% and had sufficient solubility for use in a pharmaceutical composition. The amount of water associated with this salt was calculated at about 0.5 wt % by Karl Fischer analysis and correlates with TGA and GVS analysis. The (D)-malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-4-fluorophenyl)cyclopropane-1,1-dicarboxamide will have the same properties as the (L)-malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of the N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-4-fluorophenyl)cyclopropane-1,1-dicarboxamide. For example, the hydrochloride salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-4-fluorophenyl)cyclopropane-1,1-dicarboxamide exhibits undesirable moisture sensitivity, changing phase upon exposure to high humidity (75% humidity) and high temperature (40° C.). The maleate salt had low solubility. The tartrate salt had low crystallinity and low solubility. The phosphate salt exhibited an 8% weight gain due to absorption of H₂O—the highest among the salts tested.

The water solubility of the various salts was determined using 10 mg solids per mL water. The salts were prepared in a salt screen by reacting an acetone solution of the freebase with stock tetrahydrofuran (THF) solutions of a range of acids in about a 1:1 molar ratio. Table 1 below summarizes the water solubility and other data relating to the free base and each salt.

TABLE 1

	Solubility (mg/ml)
Free base	<<0.001 very low solubility
Propionate	<<0.001 no salt formation; mixture of free base and acid
Acetate	<<0.001 no salt formation; mixture of free base and acid
Succinate	0.010 no salt formation; mixture of free base and acid
Benzoate	0.005 no salt formation; mixture of free base and acid
L-Lactate	0.015 Amorphous, salt
Pyrrolidine- carboxylate	0.44 Amorphous, salt
Glycolate	0.016 Amorphous, salt
L- Ascorbate	0.053 low crystallinity
Sulfate	0.004 Crystalline salt, low solubility
Tosylate	0.007 Crystalline salt, low solubility
Malonate	0.003 Crystalline salt, low solubility

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TABLE 1-continued

	Solubility (mg/ml)	
5 2,5dihy- droxy- benzoate	<<0.001	Crystalline Salt, low solubility
Fumarate	0.008	Crystalline Salt, low solubility
Citrate	0.002	Crystalline Salt, low solubility
Mesylate	0.175	Crystalline Salt; possible sulfonic acid formation when made with alcohol
10 Esylate	0.194	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Benzene- sulfonate	0.039	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Chloride	0.070	Crystalline but Hygroscopic; possible hydrate formation. Change in XRPD pattern upon exposure to humidity.
15 Maleate	0.005	Crystalline salt, possible hydrate formation; low solubility; different XRPD pattern observed upon scale up (possible polymorphism issue)
Phosphate	0.026	Crystalline but Hygroscopic.
L-Tartrate	0.014	Low degree of crystallinity; Hygroscopic.
(L)-Malate	0.059	Crystalline, non-Hygroscopic with no indication of hydrate formation. Suitable solubility, and chemical/physical stability.

Another aspect of this disclosure relates to crystalline forms of Compound (I), which include the N-1 and/or the N-2 crystalline form of Compound (I) as described herein. Each of form of Compound (I) is a separate aspect of the disclosure. Similarly, another aspect of this disclosure relates to crystalline forms of Compound (II), which include the N-1 and/or the N-2 crystalline form of Compound (II) as described herein. Each of which is also a separate aspect of the disclosure. As is known in the art, the crystalline (D) malate salt will form the same crystalline form and have the same properties as crystalline Compound (I). See WO 2008/083319, which discusses the properties of crystalline enantiomers. Mixtures of the crystalline forms of Compounds (I) and (II) are another aspect of the disclosure.

The crystalline N-1 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

- (i) a solid state ¹³C NMR spectrum with peaks at 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm;
 - (ii) a solid state ¹³C NMR spectrum substantially in accordance with the pattern shown in FIG. 2;
 - (iii) an x-ray powder diffraction pattern (CuK α $\lambda=1.5418 \text{ \AA}$) comprising four or more peaks selected from: 6.4, 9.0, 12.0, 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and $27.6^{\circ} 2\theta \pm 0.2^{\circ}$ 20, wherein measurement of the crystalline form is at an ambient room temperature;
 - (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 1;
 - (v) a solid state ¹⁵N NMR spectrum with peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm; and/or
 - (vi) a solid state ¹⁵N NMR spectrum substantially in accordance with the pattern shown in FIG. 3.
- Other solid state properties which may be used to characterize the crystalline N-1 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below. For crystalline Compound (I), the solid state phase and the degree of crystallinity remained unchanged after exposure to 75% RH at 40° C. for 1 week.

65 The crystalline N-2 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

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- (i) a solid state ^{13}C NMR spectrum with peaks at 23.0, 25.9, 38.0, 54.4, 56.11, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ± 0.2 ppm;
- (ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. 9;
- (iii) an x-ray powder diffraction pattern ($\text{CuK}\alpha \lambda=1.5418 \text{\AA}$) comprising four or more peaks selected from: 6.4, 9.1, 12.0, 12.8, 13.7, 17.1, 20.9, 21.9, 22.6, and 23.7 $0.2^\circ 2\theta$ 20, wherein measurement of the crystalline form is at an ambient room temperature;
- (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 8;
- (v) a solid state ^{15}N NMR spectrum with peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm; and/or
- (vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. 10.

Other solid state properties which may be used to characterize the crystalline N-2 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below.

In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-1 form.

In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-2 form.

The disclosure also relates to amorphous forms of Compounds (I) and (II). The preparation and solid state properties and characteristics of the amorphous form of Compound (I) are described in the examples below. The amorphous forms of Compounds (I) and (II) represent another aspect of the disclosure.

One further aspect of the disclosure relates to mixtures of Compound (I) and Compound (II). The mixtures may have from greater than zero weight % to less than 100 weight % Compound (I) and from less than 100 weight % to greater than zero weight % Compound (II), based on the total weight of Compound (I) and Compound (II). In other embodiments, the mixture comprises from about 1 to about 99 weight % Compound (I) and from about 99 to about 1 weight % Compound (II), based on the total weight of Compound (I) and Compound (II) in said mixture. In a further embodiment, the mixture comprises from about 90 weight % to less than 100 weight % Compound (I) and from greater than zero weight % to about 10 weight % Compound (II), based on the total weight of Compound (I) and Compound (II). Accordingly, the mixture may have 1-10% by weight of Compound (I); 11-20% by weight of Compound (I); 21-30% by weight of Compound (I); 31-40% by weight of Compound (I); 41-50% by weight of Compound (I); 51-60% by weight of Compound (I); 61-70% by weight of Compound (I); 71-80% by weight of Compound (I); 81-90% by weight of Compound (I); or 91-99% by weight of Compound (I) with the remaining weight percentage of malate salt being that of Compound (II).

Another aspect of this disclosure relates to crystalline forms of (DL)-malate salt of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, Compound (III). The (DL)-malate salt is prepared from racemic malic acid. The crystalline N-1 form of Compound (III) as described here may be characterized by at least one of the following:

- (i) a solid state ^{13}C NMR spectrum with four or more peaks selected from 20.8, 26.2, 44.8, 55.7, 70.7, 100.4,

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- 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, 182.1 ppm, ± 0.2 ppm;
- (ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. 16;
- (iii) a powder x-ray diffraction pattern ($\text{CuK}\alpha \lambda=1.5418 \text{\AA}$) comprising four or more 20 values selected from: 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6, $\pm 0.2^\circ 2\theta$, wherein measurement of the crystalline form is at temperature of room temperature;
- (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 15;
- (v) a solid state ^{15}N NMR spectrum with peaks at 119.6, 134.7, and 175.5 ppm, ± 0.2 ppm; and/or
- (vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. 17.

Other solid state properties which may be used to characterize the crystalline N-1 form of Compound (III) are shown in the figures and discussed in the examples below. In one embodiment, the N-1 Form of Compound (III) is characterized by unit cell parameters approximately equal to the following:

Cell dimensions: $a=14.60 \text{\AA}$

$b=5.20 \text{\AA}$

$c=39.09 \text{\AA}$

$\alpha=90.0^\circ$

$\beta=90.4^\circ$

$\gamma=90.0^\circ$

Space group: $P2_1/n$

Molecules of Compound (I)/unit cell: 4

Volume=2969 \AA^3

Density (calculated)=1.422 g/cm³

The unit cell parameters of Form N-1 of Compound (III) were measured at temperature of approximately 25° C., e.g., ambient or room temperature.

Each of the N-1 and N-2 crystalline forms of Compounds (I) and (II) and the crystalline form N-1 of Compound (III) have unique characteristics that can distinguish them one from another. These characteristics can be understood by comparing the physical properties of the solid state forms which are presented in the Examples below. For example, Table 2 lists characteristic XRPD peak positions ($2\theta=0.2^\circ 2\theta$) for crystalline Compound (III), Form N-1 and Forms N-1 and N-2 of crystalline Compound (I). Amorphous forms do not display reflection peaks in their XRPD patterns.

TABLE 2

Characteristic diffraction peak positions (degrees $2\theta = 0.2$) @ RT, based on pattern collected with a diffractometer ($\text{CuK}\alpha$) with a spinning capillary.		
Compound (I) Form N-1	Compound (I) Form N-2	Compound (III) Form N-1
6.4	6.4	6.4
9.0	9.1	9.1
12.0	12.0	12.1
12.8	12.8	12.8
13.5	13.7	13.6
16.9	17.1	17.1
19.4*	20.9*	19.3
21.5*	21.9*	21.4
22.8*	22.6	22.8
25.1*	23.7	25.1
27.6*	—	27.6

*unique reflections between Compound (I), Form N-1 and Compound (I), Form N-2.

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The unique reflections between Forms N-1 and N-2 of crystalline Compound (II) are designated by an asterisk (*). As discussed above, Compound (II) is an enantiomer of Compound (I) and thus, Compound (II), Form N-1 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-1. Likewise, Compound (II), Form N-2 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-2. Compounds (I) and (II) are distinct from one another based on their absolute stereochemistry, i.e., the (L)-malate salt versus the (D)-malate salt, respectively. Crystalline Compound (III), Form N-1, is distinct as the (D,L)-malate salt.

The characteristic peaks from the solid state NMR may also serve to distinguish the crystalline and amorphous forms disclosed herein. For example, Table 3 lists characteristic solid state ¹³C NMR peaks for crystalline Compound (III), Form N-1; crystalline Compound (I), Forms N-1 and N-2, and the amorphous form of Compound (I).

TABLE 3

Solid State Carbon-13 NMR Resonances (ppm, ±0.2 ppm)			
(I), Form N-1	(I), Form N-2	(III), Form N-1	(I), Amorphous
18.1	23.0	20.8	97.2
42.9	25.9	26.2	33.8
44.5	38.0	44.8	142.9
54.4	54.4	70.7	—
56.1	56.1	114.7	—
70.4	41.7	141.1	—
123.2	69.7	145.7	—
156.2	102.0	176.3	—
170.8	122.5	182.1	—
175.7	177.3	—	—
182.1	179.3	—	—
—	180.0	—	—
—	180.3	—	—

The solid state ¹⁹F and ¹⁵N NMR spectra, discussed below, provide data for similar comparison and characterization. As discussed above, being an enantiomer of Compound (I), crystalline Form N-1 and N-2 and the amorphous form of Compound (II) will have the same solid state NMR resonances, and unique peaks between them, as those listed in Table 3 for Forms N-1 and N-2 of crystalline Compound (I). Pharmaceutical Compositions and Methods of Treatment

Another aspect of this disclosure relates to a pharmaceutical composition comprising at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient. The amount of Compound (I), Compound (II), Compound (III), or the combinations thereof in the pharmaceutical composition can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may individually be present in the pharmaceutical composition as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a solid or dispersion pharmaceutical composition comprising at least one of a therapeutically effective amount of a crystalline form of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient.

Another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof at least one of Compound (I), Compound (II),

Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms, with crystalline Compound (I), Form N-1 or N-2 being preferred. Accordingly another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) or combinations thereof are present in a crystalline form. In another aspect of this disclosure, the method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer (including astrocytic tumor, which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components), lung cancer (including non-small cell lung cancer), bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, lymphoma, solid tumors, Hodgkin's disease, non-Hodgkin's lymphoma or thyroid cancer thyroid cancer (including medullary thyroid cancer).

Tyrosine kinase inhibitors have also been used to treat non-small cell lung cancer (NSCLC). Gefitinib and erlotinib are angiogenesis inhibitors that target receptors of an epidermal growth factor called tyrosine kinase. Erlotinib and Gefitinib are currently being used for treating NSCLC. Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]phenyl)-N-(4-fluorophenoxy)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof, optionally in combination with Erlotinib or Gefitinib. In another embodiment, the combination is with Erlotinib.

Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof

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such as discussed above. In another embodiment, the combination administered in this method is Erlotinib with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof.

Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-[6,7-bis(methoxy)quinolin-4-yloxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating an astrocytic tumor comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment N-(4-[6,7-bis(methoxy)quinolin-4-yloxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof. The amount administered can be a therapeutically effective amount.

Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating thyroid cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, at least one of Compound (I), Compound (II), Compound (III) or combi-

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nations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms.

Accordingly another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, a crystalline form of Compound (I), Compound (II), or any combination of Compound (I) and (II). The amount of Compound (I), Compound (II), or any combination of Compound (I) and (II) administered can be a therapeutically effective amount.

Another aspect of this disclosure relates to a use of the N-(4-[6,7-bis(methoxy)quinolin-4-yloxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate salt according to any of the above embodiments for the manufacture of a medicament for the treatment of a disease or disorder discussed above. When dissolved, a crystalline or amorphous form according to this disclosure loses its solid state structure, and is therefore referred to as a solution of, for example, Compound (I). At least one crystalline form disclosed herein may be used to prepare at least one liquid formulation in which at least one crystalline form according to the disclosure is dissolved and/or suspended.

A pharmaceutical composition such as discussed above may be any pharmaceutical form which contains active Compound (I), Compound (II) and/or Compound (III), including the solid state forms thereof (hereinafter referred to as active compound(s)). The pharmaceutical composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. The pharmaceutical compositions generally contain about 1% to about 99% by weight of the active compound(s), or a crystalline form of the active compound(s), and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of active compound, with the rest being suitable pharmaceutical excipients or other adjuvants, as discussed below.

A "therapeutically effective amount" of the active compounds, or a crystalline or amorphous form of the active compound(s), according to this disclosure to inhibit, regulate and/or modulate the signal transduction of kinases (discussed here concerning the pharmaceutical compositions) refers to an amount sufficient to treat a patient suffering from any of a variety of cancers associated with abnormal cell proliferation and angiogenesis. A therapeutically effective amount according to this disclosure is an amount therapeutically useful for the treatment or prevention of the disease states and disorders discussed herein. Compounds (I), (II), and/or (III) (including their solid state forms), possess therapeutic activity to inhibit, regulate and/or modulate the signal transduction of kinases such as described in WO2005-

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030140. N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The actual amount required for treatment of any particular patient will depend upon a variety of factors including the disease state being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex and diet of the patient; the mode of administration; the time of administration; the route of administration; and the rate of excretion of the active compound(s), or a crystalline form of the active compound(s), according to this disclosure; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J. Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference. The active compound(s), or a crystalline form of active compound(s), according to this disclosure and pharmaceutical compositions comprising them, may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. They may also be formulated with one or more of such agents in a single pharmaceutical composition.

Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends partly upon the desired method of administration to be used. For a pharmaceutical composition of this disclosure, that is, one of the active compound(s), or a crystalline form of the active compound(s), of this disclosure, a carrier should be chosen so as to substantially maintain the particular form of the active compound(s), whether it would be crystalline or not. In other words, the carrier should not substantially alter the form the active compound(s) are. Nor should the carrier be otherwise incompatible with the form of the active compound(s), such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

The pharmaceutical compositions of this disclosure may be prepared by methods known in the pharmaceutical formulation art, for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). In a solid dosage forms Compound (I) is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

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Pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of this disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. If desired, a pharmaceutical composition of this disclosure may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and antioxidants, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, and butylalated hydroxytoluene.

Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the active compound(s), or a crystalline form of the active compound(s), with, for example, suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

Because the active compound(s), or a crystalline form of the active compound(s), is maintained during their preparation, solid dosage forms are preferred for the pharmaceutical composition of this disclosure. Solid dosage forms for oral administration, which includes capsules, tablets, pills, powders, and granules, are particularly preferred. In such solid dosage forms, the active compound(s) mixed with at least one inert, pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier). Administration of the active compound(s), or a crystalline form of the active compound(s), in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. One preferable route of administration is oral administration, using a convenient dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

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General Preparation Methods of Crystalline Forms

Crystalline forms may be prepared by a variety of methods including, but not limited to, for example, crystallization or recrystallization from a suitable solvent mixture; sublimation; growth from a melt; solid state transformation from another phase; crystallization from a supercritical fluid; and jet spraying. Techniques for crystallization or recrystallization of crystalline forms of a solvent mixture include, but are not limited to, for example, evaporation of the solvent; decreasing the temperature of the solvent mixture; crystal seeding of a supersaturated solvent mixture of the compound and/or salt thereof; crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof; freeze drying the solvent mixture; and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S. R. Byrn, R. R. Pfeiffer, and J. G. Stowell, 2nd Edition, SSCI, West Lafayette, Ind. (1999).

In a crystallization technique in which solvent is employed, the solvent(s) are typically chosen based on one or more factors including, but not limited to, for example, solubility of the compound; crystallization technique utilized; and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution to which antisolvent is then added to decrease the solubility of the Compound (I) in the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

In one method that can be used in preparing crystals, Compound (I), Compound (II) and/or Compound (III) can be suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed Cooling Batch Crystallizers," J. W. Mullin and J. Nyvlt, Chemical Engineering Science, 1971, 26, 3690377. In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing large crystals, or by microcrystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

A cooled crystallization mixture may be filtered under vacuum and the isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization solvent. After being washed, the product may be dried under a nitrogen purge to afford the desired crystalline form. The

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product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, for example, differential scanning calorimetry (DSC); x-ray powder diffraction (XRPD); and thermogravimetric analysis (TGA) to assure the crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 wt. % isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 wt. % isolated yield. Optionally, the product may be delumped by being compiled or passed through mesh screen.

The features and advantages of this disclosure may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of this disclosure that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof. The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference. All measurements are subject to experimental error and are within the spirit of the invention.

As used herein, "amorphous" refers to a solid form of a molecule and/or ion that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern with sharp maxima.

As used herein, the term "substantially pure" means the crystalline form of Compound (I) referred to contains at least about 90 wt. % based on the weight of such crystalline form. The term "at least about 90 wt. %," while not intending to limit the applicability of the doctrine of equivalents to the scope of the claims, includes, but is not limited to, for example, about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99 and about 100% wt. %, based on the weight of the crystalline form referred to. The remainder of the crystalline form of Compound (I) may comprise other Form(s) of Compound (I) and/or reaction impurities and/or processing impurities that arise, for example, when the crystalline form is prepared. The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectroscopy, and/or infrared spectroscopy.

PREPARATIVE EXAMPLES

Example 1: Preparation of N-(4-[6,7-bis(methoxy)quinolin-4-yloxy]phenyl)-N¹(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt Thereof (Compound (I))

The synthetic route used for the preparation of N-(4-[6,7-bis(methoxy)quinolin-4-yloxy]phenyl)-N¹(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 1:

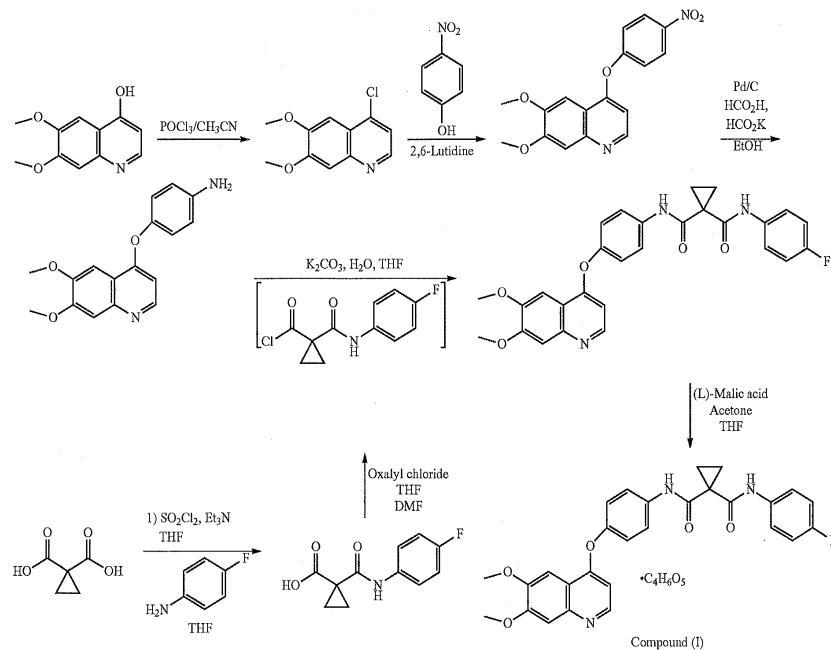
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SCHEME 1



The process shown in Scheme 1 is described in more detail below.

1.1 Preparation of 4-Chloro-6,7-dimethoxy-quinoline

A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (1 L, 10.0 kg) and acetonitrile (64.0 L). The resulting mixture was heated to approximately 65° C. and phosphorus oxychloride (POCl_3 , 50.0 kg) was added. After the addition of POCl_3 , the temperature of the reaction mixture was raised to approximately 80° C. The reaction was deemed complete (approximately 9.0 hours) when <2% of the starting material remained (in process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 10° C. and then quenched into a chilled solution of dichloromethane (DCM, 238.0 kg), 30% NH_4OH (135.0 kg), and ice (440.0 kg). The resulting mixture was warmed to approximately 14° C., and phases were separated. The organic phase was washed with water (40.0 kg) and concentrated by vacuum distillation with the removal of solvent (approximately 190.0 kg). Methyl-t-butyl ether (MTBE, 50.0 kg) was added to the batch, and the mixture was cooled to approximately 10° C., during which time the product crystallized out. The solids were recovered by centrifugation, washed with n-heptane (20.0 kg), and dried at approximately 40° C. to afford the title compound (8.0 kg).

1.2 Preparation of 6,7-Dimethyl-4-(4-nitro-phenoxy)-quinoline

A reactor was sequentially charged with 4-chloro-6,7-dimethoxy-quinoline (8.0 kg), 4 nitrophenol (7.0 kg), 4 dimethylaminopyridine (0.9 kg), and 2,6 lutidine (40.0 kg). The reactor contents were heated to approximately 147° C. When the reaction was complete (<5% starting material remaining as determined by in process HPLC analysis, approximately 20 hours), the reactor contents were allowed to cool to approximately 25° C. Methanol (26.0 kg) was added, followed by potassium carbonate (3.0 kg) dissolved in water (50.0 kg). The reactor contents were stirred for approximately 2 hours. The resulting solid precipitate was filtered, washed with water (67.0 kg), and dried at 25° C. for approximately 12 hours to afford the title compound (4.0 kg).

1.3 Preparation of 4-(6,7-Dimethoxy-quinoline-4-yloxy)-phenylamine

A solution containing potassium formate (5.0 kg), formic acid (3.0 kg), and water (16.0 kg) was added to a mixture of 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline (4.0 kg), 10% palladium on carbon (50% water wet, 0.4 kg) in tetrahydrofuran (40.0 kg) that had been heated to approximately 60° C. The addition was carried out such that the temperature of the reaction mixture remained approximately 60° C. When the reaction was deemed complete as determined using in-

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process HPLC analysis (<2% starting material remaining, typically 15 hours), the reactor contents were filtered. The filtrate was concentrated by vacuum distillation at approximately 35° C. to half of its original volume, which resulted in the precipitation of the product. The product was recovered by filtration, washed with water (12.0 kg), and dried under vacuum at approximately 50° C. to afford the title compound (3.0 kg; 97% AUC).

1.4 Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid

Triethylamine (8.0 kg) was added to a cooled (approximately 4° C.) solution of commercially available cyclopropane-1,1-dicarboxylic acid (21, 10.0 kg) in THF (63.0 kg) at a rate such that the batch temperature did not exceed 10° C. The solution was stirred for approximately 30 minutes, and then thionyl chloride (9.0 kg) was added, keeping the batch temperature below 10° C. When the addition was complete, a solution of 4-fluoroaniline (9.0 kg) in THF (25.0 kg) was added at a rate such that the batch temperature did not exceed 10° C. The mixture was stirred for approximately 4 hours and then diluted with isopropyl acetate (87.0 kg). This solution was washed sequentially with aqueous sodium hydroxide (2.0 kg dissolved in 50.0 L of water), water (40.0 L), and aqueous sodium chloride (10.0 kg dissolved in 40.0 L of water). The organic solution was concentrated by vacuum distillation followed by the addition of heptane, which resulted in the precipitation of solid. The solid was recovered by centrifugation and then dried at approximately 35° C. under vacuum to afford the title compound. (10.0 kg)

1.5 Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride

Oxalyl chloride (1.0 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (2.0 kg) in a mixture of THF (11 kg) and N, N-dimethylformamide (DMF; 0.02 kg) at a rate such that the batch temperature did not exceed 30° C. This solution was used in the next step without further processing.

1.6 Preparation of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

The solution from the previous step containing 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride was added to a mixture of 4-(6,7-dimethoxy-quinoline-4-yl)oxy-phenylamine (3.0 kg) and potassium carbonate (4.0 kg) in THF (27.0 kg) and water (13.0 kg) at a rate such that the batch temperature did not exceed 30° C. When the reaction was complete (in typically 10 minutes), water (74.0 kg) was added. The mixture was stirred at 15-30° C. for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a premade solution of THE (11.0 kg) and water (24.0 kg), and dried at approximately 65° C. under vacuum for approximately 12 hours to afford the title compound (free base, 5.0 kg). ¹H NMR (400 MHz, d₆-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H),

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7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15 (m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H=502.

1.7 Preparation of N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L) malate salt (Compound (I))

A solution of (L)-malic acid (2.0 kg) in water (2.0 kg) was added to a solution of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yl)oxy]-phenyl-amide (4-fluoro-phenyl)-amide free base (15, 5.0 kg) in ethanol, maintaining a batch temperature of approximately 25° C. Carbon (0.5 kg) and thiol silica (0.1 kg) were then added, and the resulting mixture was heated to approximately 78° C., at which point water (6.0 kg) was added. The reaction mixture was then filtered, followed by the addition of isopropanol (38.0 kg), and was allowed to cool to approximately 25° C. The product was recovered by filtration and washed with isopropanol (20.0 kg) and dried at approximately 65° C. to afford Compound (I) (5.0 kg).

Example 2: Preparation of Crystalline Compound (I), Form N-1

A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60° C. and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through

35 a Polish Filter.

At 60° C., acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60° C. for 10 hours. The solution was then cooled to 20° C. and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR; 1.20 L). The solids were dried at 60° C. (25 mm Hg) for 6 hours to afford Compound (I), Form N-1 (108 g; 0.85 equiv; 108.00 g; 85.22% yield) as a white crystalline solid.

Example 3: Alternate Preparation of Crystalline Compound (I), Form N-1

A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 50 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 h with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

Separately, a powder blend was made with known amounts of two batches of Compound (I): (1) 300 mg of batch 1, which contained approximately 41% Compound (I), 60 Form N-1 and 59% Compound (I), Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to Compound (I), Form N-2.

The Compound (I), Form N-1 and Compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet

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cake. The wet cake was dried in a vacuum oven at 45° C. to afford 128 mg of crystalline Compound (I) in the N-1 form.

Example 4: Preparation of Crystalline Compound (I), Form N-2

4.1 Preparation of Crystalline Compound (I), Form N-2 Seed Crystals

A solution was prepared by combining 20 ml of acetone and 300 mg of freebase N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide in a 25 ml screw capped vial. Next, 0.758 ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hr at ambient temperature. The sample was then suction filtered with 0.45 µm PTFE filter cartridge and dried in vacuo at ambient temperature overnight.

4.2 Preparation of Crystalline Compound (I), Form N-2

To a reactor were added N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50° C. Seed crystals were added (1%, 480 mg) and the malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 mL/min (3 h)). The slurry was held at 50° C. for 18 h and then was cooled to 25° C. over 30 min. The solids were filtered, and washed with 20% THF/MIBK (10V, 150 mL). The solids were dried under vacuum at 60° C. for 5 h to afford Compound (I) (55.7 g; 0.92 equiv; 55.70 g; 91.56% yield) as an off-white crystalline solid.

Example 5: Preparation of Crystalline Compound (III), Form N-1

A one mL aliquot (DL)-malic acid salt of N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, slurried in tetrahydrofuran (THF), was heated to 60° C. on a hot-plate in a half-dram vial. Next, tetrahydrofuran was added drop-wise until an almost clear solution was obtained. The vial was capped, removed from the hot plate and equilibrated at ambient temperature without agitation. Crystallization was apparent after several hours and the solution was allowed to stand overnight to allow completion. Several droplets of the resulting slurry were placed on a glass slide for microscopic analysis. The crystalline material consisted of many elongated plates ranging up to 60 microns in the longest dimension.

Alternate Preparation of Crystalline Compound (III), Form N-1

To a reactor were added N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-

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1,1-dicarboxamide (15 g; 1.00 equiv; 15.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (DL)-malic acid (1.2 equiv (molar); 4.53 g) was dissolved into methyl isobutyl ketone (8 mL/g-bulk-LR; 120.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 15.00 mL). Next, 20 mL of the solution was added to the first solution at 50° C. The malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 mL/min (3 h)). The slurry was held at 50° C. for 18 h and then was cooled to 25° C. over 30 min. The solids were filtered, and washed with 20% THF/MIBK (10V, 150 mL). The solids were dried under vacuum at 60° C. for 5 h to afford Compound (III) (15.52 g; 86.68% yield) as an off-white solid.

Example 6: Preparation of Amorphous Compound (I)

A solution was prepared with 5 g of N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate and 250 mL of a 1:1 (v:v) mixture of methanol and dichloromethane. The hazy solution was filtered through a 0.45 micron filter to yield a clear, yellowish solution. The solution was pumped through the spray dryer nozzle at a rate of 12.9 cc/min, and was atomized by nitrogen gas fed at a rate of 10.911 min. The temperature at the inlet of the cyclone was set to 65° C. to dry the wet droplets. Dry amorphous powder (1.5 g) was collected (yield=30%).

CHARACTERIZATION EXAMPLES

**I. NMR Spectra in Dimethyl Sulfoxide Solution
I.1 Compound (I), Form N-1**

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, 1H, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

I.2 Compound (I), Form N-2

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

I.3 Compound (III), Form N-1

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

I.4 Compound (III), Form N-2

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48

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¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

Characterization of Solid State Forms of N-(4-{[6,7-bis (methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate

II. Powder X-Ray Diffraction (XRPD) Studies

X-Ray Powder Diffraction (XRPD) patterns were collected on a Bruker AXS C2 GADDS diffractometer equipped with an automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. The radiation source used was copper (Cu K α =1.5406 Å), wherein the voltage was set at 40 kV and the current was set at 40 mA, X-ray optics consists of a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm. The beam divergence, i.e. the effective size of the X-ray beam on the sample, was approximately 4 mm. A 0-0 continuous scan mode was employed with a sample—detector distance of 20 cm which gives an effective 20 range of 3.2°–29.8°. Samples run under ambient conditions (from about 18° C. to about 25° C.) were prepared as flat plate specimens using powder as received without grinding. Approximately 1.2 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. Typically the sample would be exposed to the X-ray beam for 120 seconds. Beam divergence (i.e., effective size of X-ray spot, gives a value of approximately 4 mm. Alternatively, the powder samples were placed in sealed glass capillaries of 1 mm or less in diameter; the capillary was rotated during data collection at a sample-detector distance of 15 cm. Data were collected for 3<2θ<35° with a sample exposure time of at least 2000 seconds. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional XRPD pattern with a step size of 0.02°2θ in the range of 3 to 35°2θ±0.2°2θ. The software used for data collection was GADDS for WNT 4.1.16 and the data were analyzed and presented using Diffrac Plus EVA v 9.0.0.2 or v 13.0.0.2.

II.1 Compound (I), Form N-1

FIG. 1 shows the experimental XRPD pattern of crystalline Compound (I), Form N-1 acquired at room temperature (about 25° C.). A list of the peaks are shown in Table 2, above. The 2θ values at 19.4, 21.5, 22.8, 25.1, and 27.6 ($\pm 0.2^{\circ}$) are useful for characterizing crystalline Compound (I), Form N-1. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

II.2 Compound (I), Form N-2

FIG. 8 shows the experimental XRPD pattern of crystalline Compound (I), Form N-2 acquired at room temperature (about 25° C.). A list of the peaks are shown in Table 2, above. The 2θ values at 20.9 and 21.9 ($\pm 0.2^{\circ}$) are useful for characterizing crystalline Compound (I), Form N-2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

II.3 Compound (III), Form N-1

FIG. 15 shows the experimental and the simulated XRPD pattern of crystalline Compound (III), Form N-1, acquired at 25° C. using a spinning capillary sample. A list of the peaks are shown in Table 2, above. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-2.

II.4 Amorphous Compound (I)

FIG. 22 shows the experimental XRPD pattern of amorphous Compound (I) acquired at room temperature (about

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25° C.). The spectra is characterized a broad peak and the absence of sharp peaks, which is consistent with an amorphous material.

III. Single Crystal X-Ray Study for Compound (III), Form N-1

Data were collected on a Bruker-Nonius CAD4 serial diffractometer. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Intensities were measured using Cu K α radiation ($\lambda=1.5418$ Å) at a constant temperature with the 0-20 variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Alternately, single crystal data were collected on a Bruker-Nonius Kappa CCD 2000 system using Cu K α radiation ($\lambda=1.5418$ Å). Indexing and processing of the measured intensity data were carried out with the HKL2000 software package (Otwinowski, Z. & Minor, W. (1997) in Macromolecular Crystallography, eds. Carter, W. C. Jr & Sweet, R. M. (Academic, NY), Vol. 276, pp. 307-326) in the Collect program suite (Collect Data collection and processing user interface: Collect: Data collection software, R. Hooft, Nonius B. V., 1998). Alternately, single crystal data were collected on a Bruker-AXS APEX2 CCD system using Cu K α radiation ($\lambda=1.5418$ Å). Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v.27). When indicated, crystals were cooled in the cold stream of an Oxford cryo system (Oxford Cryosystems Cryostream cooler: J. Cosier and A. M. Glazer, J. Appl. Cryst., 1986, 19, 105) during data collection.

The structures were solved by direct methods and refined on the basis of observed reflections using either the SDP software package (SDP, Structure Determination Package, Enraf-Nonius, Bohemia, N.Y. 11716. Scattering factors, including f and f', in the SDP software were taken from the "International Tables for Crystallography", Kynoch Press, Birmingham, England, 1974; Vol IV, Tables 2.2A and 2.3.1) with minor local modifications or the crystallographic packages MAXUS (maxus solution and refinement software suite: S. Mackay, C. J. Gilmore, C. Edwards, M. Tremayne, N. Stewart, K. Shankland, maxus: a computer program for the solution and refinement of crystal structures from diffraction data) or SHELXTL (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27).

The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. The function minimized in the refinements was $\sum_w(|F_o| - |F_c|)^2$. R is defined as $\sum|F_o| - |F_c|/\sum|F_o|$ while $R_w = [\sum_w(|F_o| - |F_c|)^2 / \sum_w |F_o|^2]^{1/2}$ where w is an appropriate weighting function based on errors in the observed intensities. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors, but no hydrogen parameters were varied.

"Hybrid" simulated powder X-ray patterns were generated as described in the literature (Yin, S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougoutas, J. Z., *American Pharmaceutical Review*, 2003, 6, 2, 80). The room temperature cell parameters were obtained by performing a cell refinement using the CellRefine.xls program. Input to the program includes the 2-theta position of ca. 10 reflections, obtained from the experimental room temperature powder pattern; the corresponding Miller indices, hkl, were assigned based on the single-crystal data collected at low temperature. A new (hybrid) XRPD was calculated (by either of the software programs, Alex or LatticeView) by inserting the

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molecular structure determined at low temperature into the room temperature cell obtained in the first step of the procedure. The molecules are inserted in a manner that retains the size and shape of the molecule and the position of the molecules with respect to the cell origin, but, allows intermolecular distances to expand with the cell.

A single crystal, measuring 40x30x10 microns, was selected from the slurry of crystals described in Example 5 for single crystal diffraction analysis. The selected crystal was affixed to a thin glass fiber with a small amount of a light grease, and mounted at room temperature on a Bruker ApexII single crystal diffractometer equipped with a rotating copper anode.

Crystalline Compound (III), From N-1 is characterized by unit cell parameters approximately equal to those reported in Table 4. The unit cell parameters were measured at a temperature of about 25° C.

TABLE 4

a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°
Space group: P2 ₁ /n
Molecules of Compound (I)/unit cell: 4
Volume = 2969 Å ³

Structure solution and refinement were routine in the monoclinic space group, P2₁/n, with four formula units in the unit cell. The structure contains cations of N-(4-[6,7-bis(methoxy)-quinolin-4-yl]oxy)phenyl)-N'- (4-fluorophenyl)cyclopropane-1,1-dicarboxamide, protonated at the quinoline nitrogen atom, and singly ionized malic acid anions, in a1:1 ratio. Further, the crystal contained a1:1 ratio of (L)-malic acid ions to (D)-malic acid ions. Table 5 fractional atomic coordinates for Compound (III), Form N-1 calculated at a temperature of about 25° C.

Based on the single crystal X-ray data, crystalline Compound (III), Form N-1 may be characterized by a simulated powder x-ray diffraction (XRPD) pattern substantially in accordance with the simulated pattern shown in FIG. 15 and/or by an observed XRPD pattern substantially in accordance with the experimental pattern shown in FIG. 15.

TABLE 5

Fractional Atomic Coordinates for Compound (III), Form N-1
Calculated at a Temperature of about 25° C.

Atom	X	Y	Z
O1	0.30601	-0.52166	0.22875
O2	0.29518	0.12504	0.09391
O3	0.19041	-0.53232	0.18147
F5	-0.07307	2.12170	-0.08811
O6	0.18186	1.20500	-0.03241
O7	0.57137	0.22739	0.23473
O8	0.58700	-0.17911	0.24998
O9	0.41742	0.76377	-0.04319
N10	0.28649	0.82210	-0.01420
O11	0.87391	0.22086	0.31241
N12	0.46887	0.17029	0.17613
C13	0.29647	0.64886	0.01247
C14	0.31416	1.08187	-0.06304
C15	0.33900	-0.02207	0.14761
N16	0.20651	1.40640	-0.08267
C17	0.40079	-0.01723	0.17602
C18	0.29743	0.29956	0.06604
C19	0.00418	1.80556	-0.05680

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TABLE 5-continued

Atom	X	Y	Z
C20	0.11925	1.73626	-0.11097
C21	0.22556	1.24019	-0.05791
C22	0.39150	-0.17467	0.20389
C23	0.22558	0.63870	0.03619
C24	0.62714	0.39565	0.29760
C25	0.34591	0.87438	-0.03961
C26	0.36467	-0.51389	0.25773
C27	0.26562	-0.20277	0.14859
C28	0.35380	0.15272	0.12054
C29	0.07365	1.60604	-0.05443
C30	0.04897	1.92890	-0.11212
C31	0.73841	0.04517	0.28641
C32	0.32089	-0.35160	0.20385
C33	0.36641	0.29052	0.04302
C34	0.42458	0.32272	0.12143
C35	0.11723	-0.54030	0.15742
C36	0.12933	1.59042	-0.08228
C37	-0.00344	1.93494	-0.08547
C38	0.36439	0.47245	0.01586
C39	0.59040	0.05797	0.25625
C40	0.25712	-0.35516	0.17574
C41	0.63543	0.13842	0.29041
C42	0.22703	0.46640	0.06306
C43	0.34559	1.01717	-0.10021
C44	0.39312	1.20834	-0.08137
C45	0.48224	0.32340	0.15059
O46	0.77400	0.04784	0.34652
C47	0.79349	0.09920	0.31966
H10	0.22646	0.91057	-0.01479
H16	0.24790	1.42164	-0.10317
H19	-0.04176	1.82973	-0.03893
H20	0.16347	1.73025	-0.13083
H22	0.43179	-0.17902	0.22447
H23	0.17093	0.73524	0.03244
H27	0.21953	-0.24212	0.12962
H29	0.07954	1.50390	-0.03492
H30	0.04671	2.05817	-0.13354
H33	0.41851	0.16255	0.04395
H34	0.43433	0.41859	0.10106
H38	0.41440	0.45648	-0.00227
H41	0.61062	0.02238	0.31086
H42	0.17752	0.45794	0.07911
H45	0.53033	0.44239	0.15049
H31a	0.76754	0.12071	0.26693
H31b	0.74726	-0.15247	0.28137
H43a	0.30237	1.06909	-0.12187
H43b	0.36868	0.85693	-0.10836
H44a	0.45563	1.18725	-0.07495
H44b	0.38932	1.39942	-0.08846
H26a	0.35958	-0.37184	0.27147
H26b	0.42813	-0.55605	0.25348
H26c	0.34954	-0.66814	0.27571
H35a	0.08189	-0.39941	0.15398
H35b	0.06671	-0.68838	0.16269
H35c	0.13276	-0.61095	0.13323
H11	0.88836	0.21926	0.28968
H12	0.50720	0.16494	0.19477
H24	0.61522	0.45898	0.27789

IV. Solid State Nuclear Magnetic Resonance (SSNMR)
All solid-state C-13 NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and the TPPM pulse sequence and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A. E. Bennett et al, *J. Chem. Phys.*, 1995, 103, 6951), (G. Metz, X. Wu and S. O. Smith, *J. Magn. Reson. A*, 1994, 110, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance being set to 38.56 ppm (W. L. Earl and D. L. VanderHart, *J. Magn. Reson.*, 1982, 48, 35-54).

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IV.1 Compound (I), Form N-1

The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-1 is shown in FIG. 2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

SS ^{13}C NMR Peaks: 18.1, 20.6, 26.0, 42.9, 44.5, 54.4, 55.4, 56.1, 70.4, 99.4, 100.1, 100.6, 114.4, 114.9, 115.8, 119.6, 120.1, 121.6, 123.2, 124.1, 136.4, 138.6, 140.6, 145.4, 150.1, 150.9, 156.2, 157.4, 159.4, 164.9, 167.1, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm.

FIG. 3 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, 15 may be sufficient to characterize crystalline Compound (I), Form N-1.

FIG. 4 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows a peak at -121.6, -120.8, and -118.0 ppm, ± 0.2 ppm.

IV.2 Compound (I), Form N-2

The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-2 is shown in FIG. 9. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

SS ^{13}C NMR Peaks: 20.5, 21.8, 23.0, 25.9, 26.4, 38.0, 41.7, 54.7, 55.8, 56.2, 56.6, 69.7, 99.4, 100.0, 100.4, 100.8, 102.3, 114.5, 115.5, 116.7, 119.0, 120.2, 121.1, 121.2, 122.1, 122.9, 124.5, 136.0, 137.3, 138.1, 138.9, 139.5, 140.2, 144.9, 145.7, 146.1, 150.7, 156.7, 157.7, 159.6, 159.7, 165.1, 167.0, 168.0, 171.5, 177.3, 179.3, 180.0, and 180.3 ppm, ± 0.2 ppm.

FIG. 10 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, 35 may be sufficient to characterize crystalline Compound (I), Form N-2.

FIG. 11 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at -121.0 and -119.1 ppm, ± 0.2 ppm. Those peaks, individually or together, may be sufficient to characterize crystalline Compound (I), Form N-2.

IV.3 Compound (III), Form N-1

The solid state ^{13}C NMR spectrum of crystalline Compound (III), Form N-1 is shown in FIG. 16. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

SS ^{13}C NMR Peaks: 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, and 182.1 ppm, ± 0.2 ppm.

FIG. 17 shows the solid state ^{15}N NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows peaks at 119.6, 134.7, and 175.5 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, 55 may be sufficient to characterize crystalline Compound (III), Form N-1.

FIG. 18 shows the solid state ^{19}F NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows a peak at -120.5 ppm, ± 0.2 ppm.

IV.4 Compound (I), Amorphous

FIG. 23 shows the solid state ^{13}C NMR spectrum of amorphous Compound (I). The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

SS ^{13}C NMR Peaks (ppm): 12.2, 17.8, 20.3, 21.8, 27.2, 33.8, 41.7, 56.9, 69.9, 99.9, 102.2, 115.6, 122.2, 134.4,

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137.8, 142.9, 149.1, 150.9, 157.3, 159.7, 167.0, 171.7, 173.1, 177.4, and 179.5 ppm, ± 0.2 ppm.

FIG. 24 shows the solid state ^{15}N NMR spectrum of amorphous Compound (I). The spectrum shows peaks at 120.8, 131.8, 174.7, and 178.3 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

FIG. 25 shows the solid state ^{19}F NMR spectrum of amorphous Compound (I). The spectrum shows a peak at -118.9 ppm, ± 0.2 ppm.

V. Thermal Characterization Measurements

Thermal Gravimetric Analysis (TGA)

The TGA measurements were performed in a TA InstrumentsTM model Q500 or 2950, employing an open pan setup. The sample (about 10-30 mg) was placed in a platinum pan previously tared. The weight of the sample was measured accurately and recorded to a thousand of a milligram by the instrument. The furnace was purged with nitrogen gas at 100 mL/min. Data were collected between room temperature and 300° C. at 10° C./min heating rate.

Differential Scanning Calorimetry (DSC) Analysis

DSC measurements were performed in a TA InstrumentsTM model Q2000, Q1000 or 2920, employing an open pan setup. The sample (about 2-6 mg) was weighed in an aluminum pan and recorded accurately recorded to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50 mL/min. Data were collected between room temperature and 300° C. at 10° C./min heating rate. The plot was made with the endothermic peaks pointing down.

V.1 Compound (I), Form N-1

FIG. 5 shows the TGA thermogram for crystalline Compound (I), Form N-1, which shows a weight loss of approximately 0.4 weight % at a temperature of 170° C.

FIG. 6 shows the DSC thermogram for crystalline Compound (I), Form N-1, which showed a melting point of approximately 187° C.

V.2 Compound (I), Form N-2

FIG. 12 shows the TGA thermogram for crystalline Compound (I), Form N-2, which shows a weight loss of approximately 0.1 weight % at a temperature of 170° C.

FIG. 13 shows the DSC thermogram for crystalline Compound (I), Form N-2, which showed a melting point of approximately 186° C.

V.3 Compound (III), Form N-1

FIG. 19 shows the TGA thermogram for crystalline Compound (III), Form N-1, which shows a weight loss of approximately 0.2 weight % at a temperature of 170° C.

FIG. 20 shows the DSC thermogram for crystalline Compound (III), Form N-1, which showed a melting point of approximately 186° C.

V.2 Compound (I), Amorphous

FIG. 26 shows the DSC for crystalline Compound (I).

VI. Moisture Vapor Isotherm Measurements

Moisture sorption isotherms were collected in a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was dried at 60° C. until the loss rate of 0.0005 wt %/min was obtained for 10 minutes. The sample was tested at 25° C. and 3 or 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95% RH. Equilibration at each RH was reached when the rate of 0.0003 wt %/min for 35 minutes was achieved or a maximum of 600 minutes.

VI.1 Compound (I), Form N-1

FIG. 7 shows the moisture vapor isotherm of crystalline Compound (I), Form N-1.

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VI.2 Compound (I), Form N-1

FIG. 14 shows the moisture vapor isotherm of crystalline Compound (I), Form N-2.

VI.3 Compound (III), Form N-1

FIG. 21 shows the moisture vapor isotherm of crystalline Compound (III), Form N-1.

VI.4 Compound (I), Amorphous

FIG. 27 shows the moisture vapor isotherm of amorphous Compound (I).

The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but

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should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A pharmaceutical composition comprising the N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxylphenyl)-N'-4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is crystalline; and a pharmaceutically acceptable excipient.

10 2. A pharmaceutical composition comprising the N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxylphenyl)-N'-4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (DL)-malate salt and wherein said salt is crystalline; and a pharmaceutically acceptable excipient.

15 3. A pharmaceutical composition comprising the N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxylphenyl)-N'-4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or (D)-malate salt and 20 wherein said salt is crystalline; and a pharmaceutically acceptable excipient.

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(12) **United States Patent**
Brown et al.

(10) **Patent No.:** US 11,098,015 B2
(45) **Date of Patent:** *Aug. 24, 2021

(54) **MALATE SALT OF N-(4-[6,7-BIS(METHYLOXY)QUINOLIN-4-YL]OXY)PHENYL)-N'-(4-FLUOROPHENYL)CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEREOF FOR THE TREATMENT OF CANCER**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(65) **Prior Publication Data**

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(57) **ABSTRACT**

Disclosed are malate salts of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including a (L)-malate salt, a (D)-malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

3 Claims, 27 Drawing Sheets

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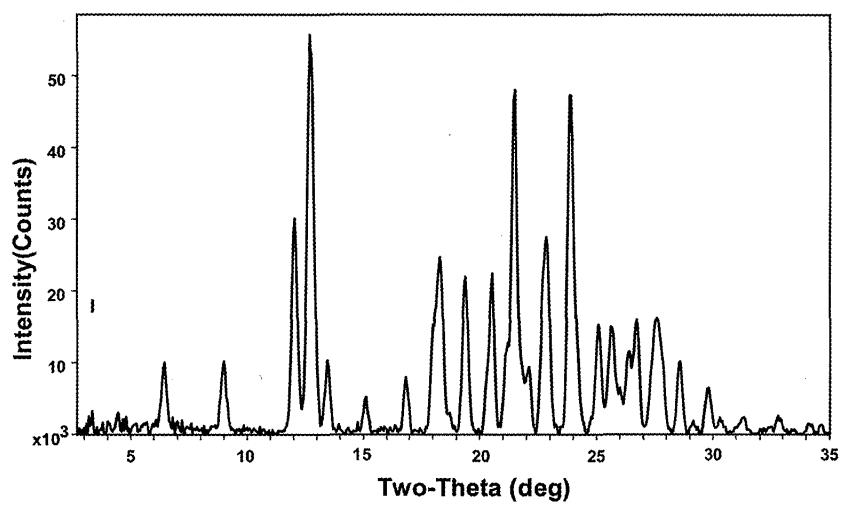
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Figure 1



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Appx197

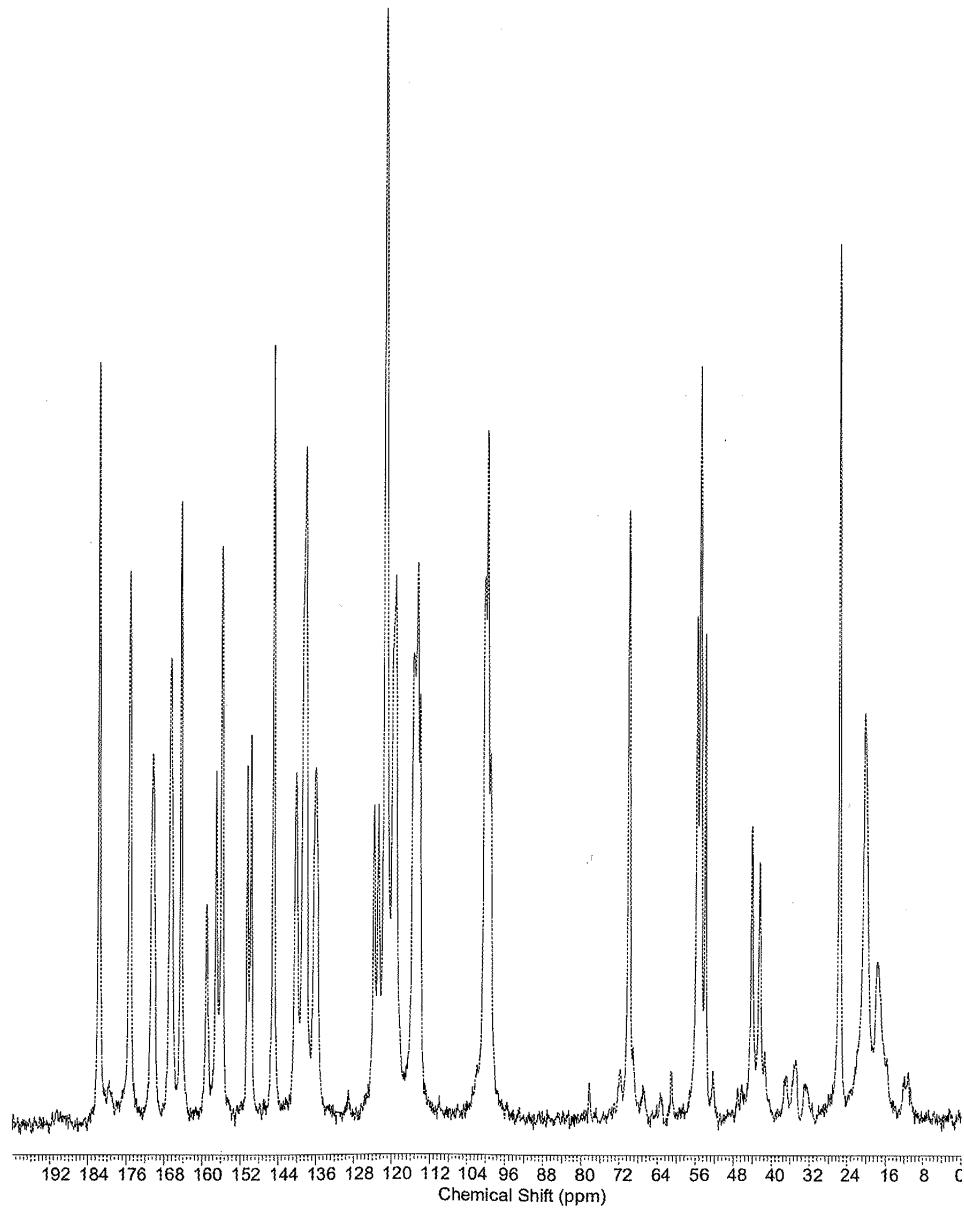
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Figure 2



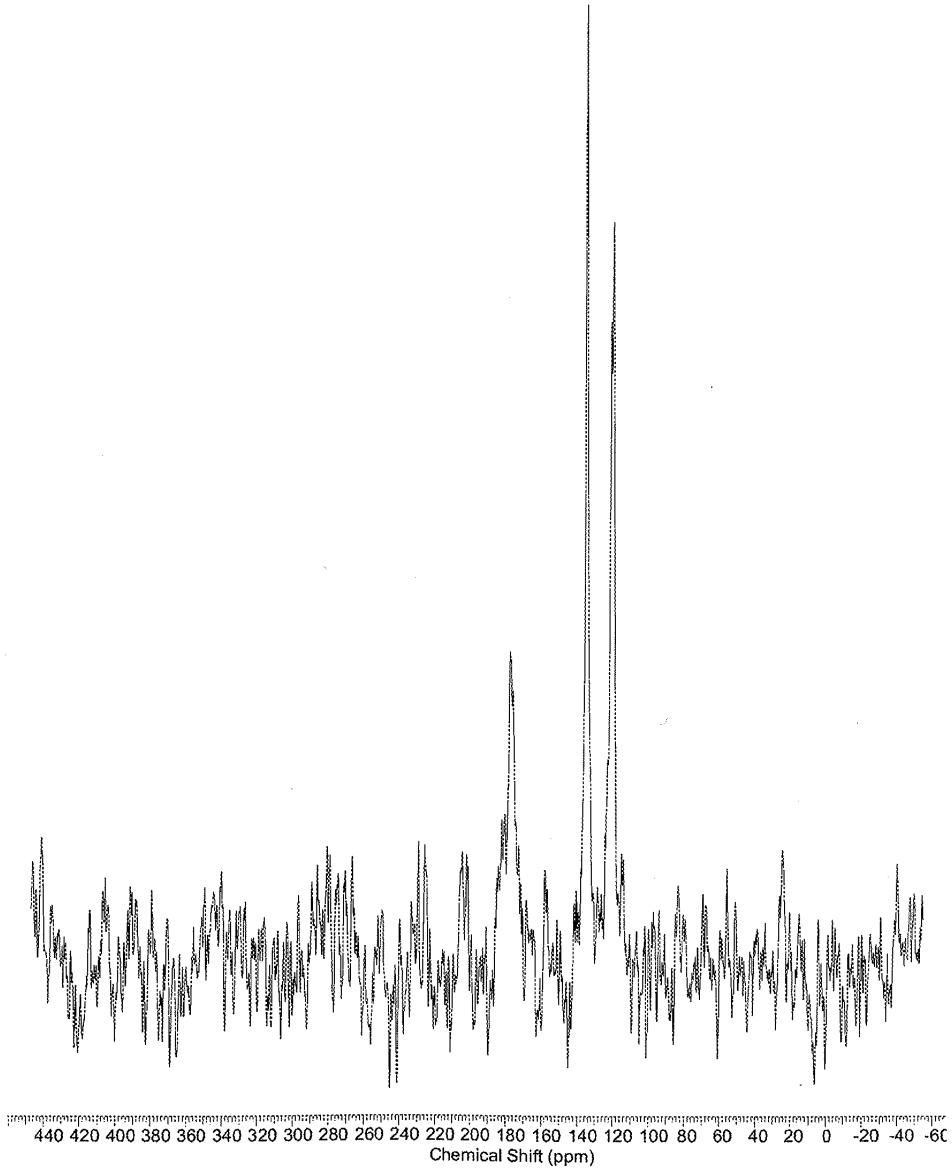
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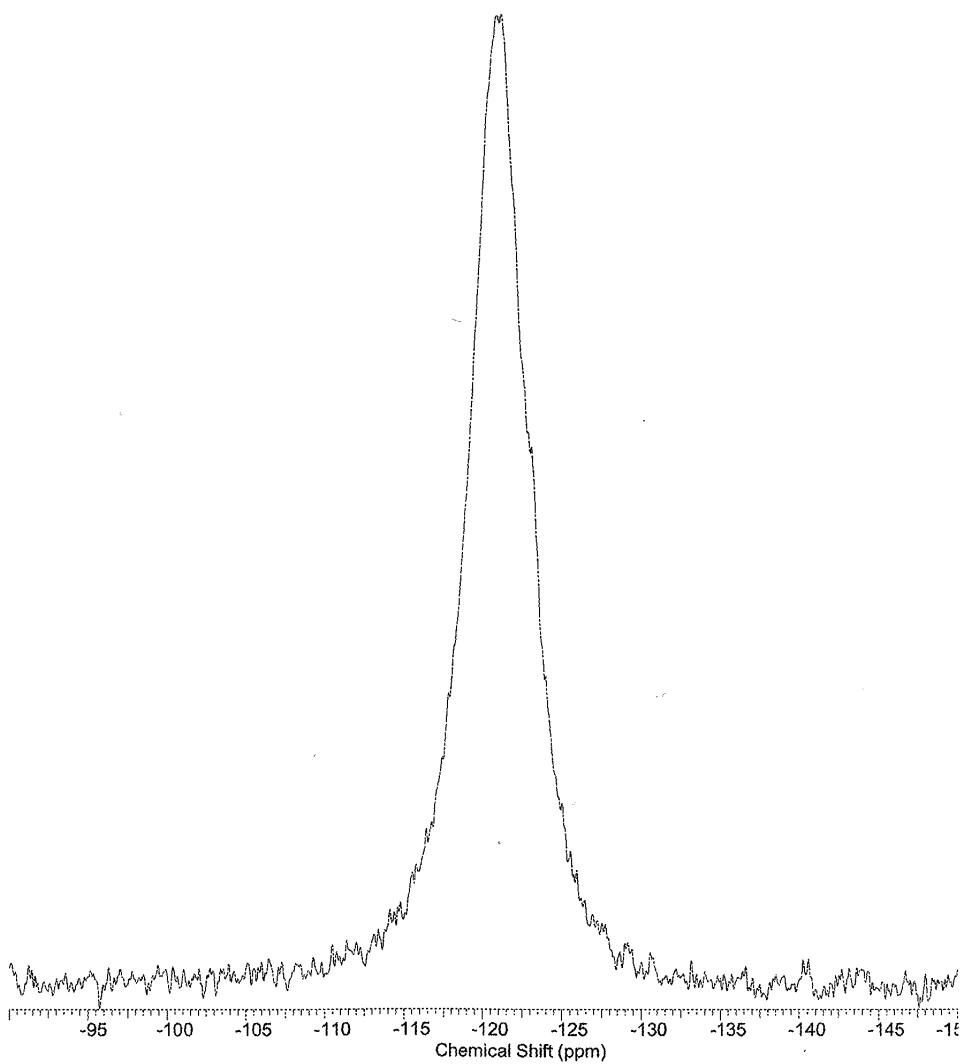
Figure 3



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Figure 4



EXEL2_00132140

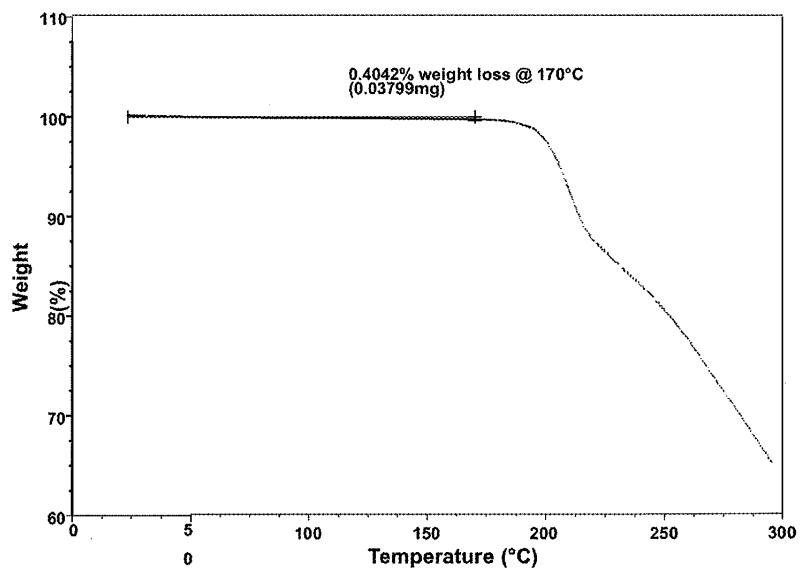
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Appx200

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Figure 5

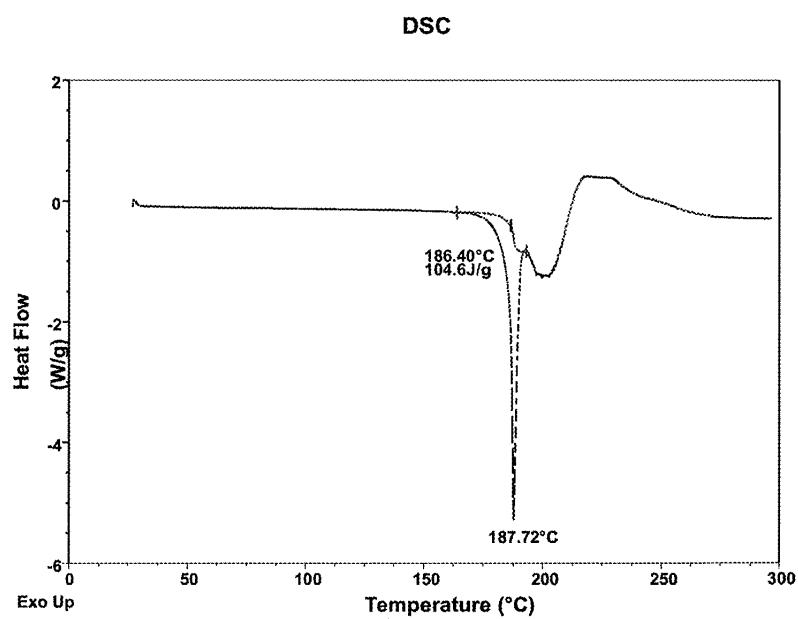
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EXEL2_00132141

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Figure 6



EXEL2_00132142

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Appx202

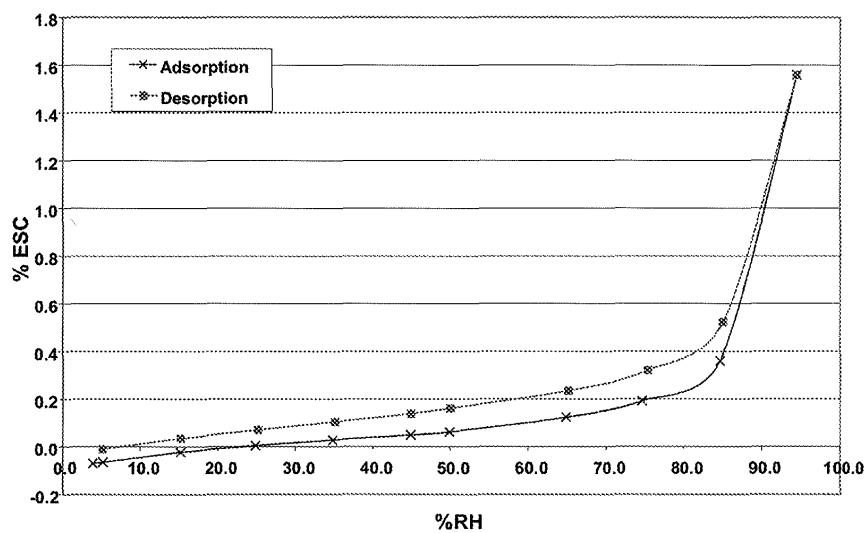
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Figure 7



Moisture Sorption of Compound (I), Form N-1

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Appx203

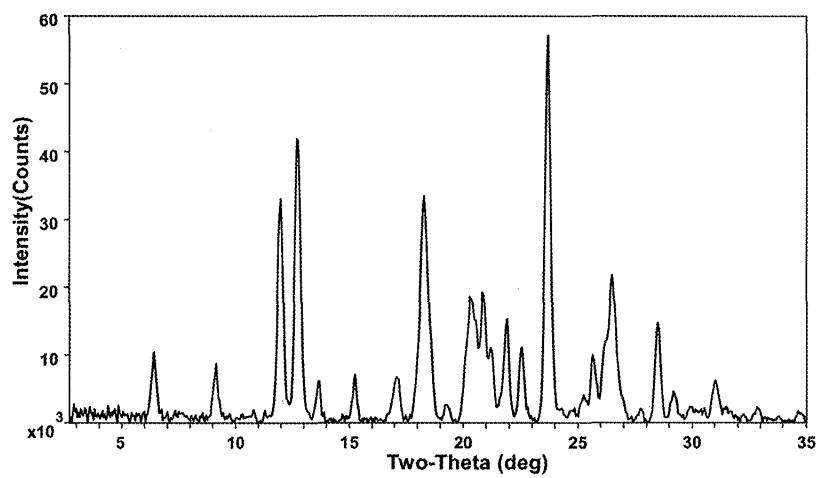
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Figure 8



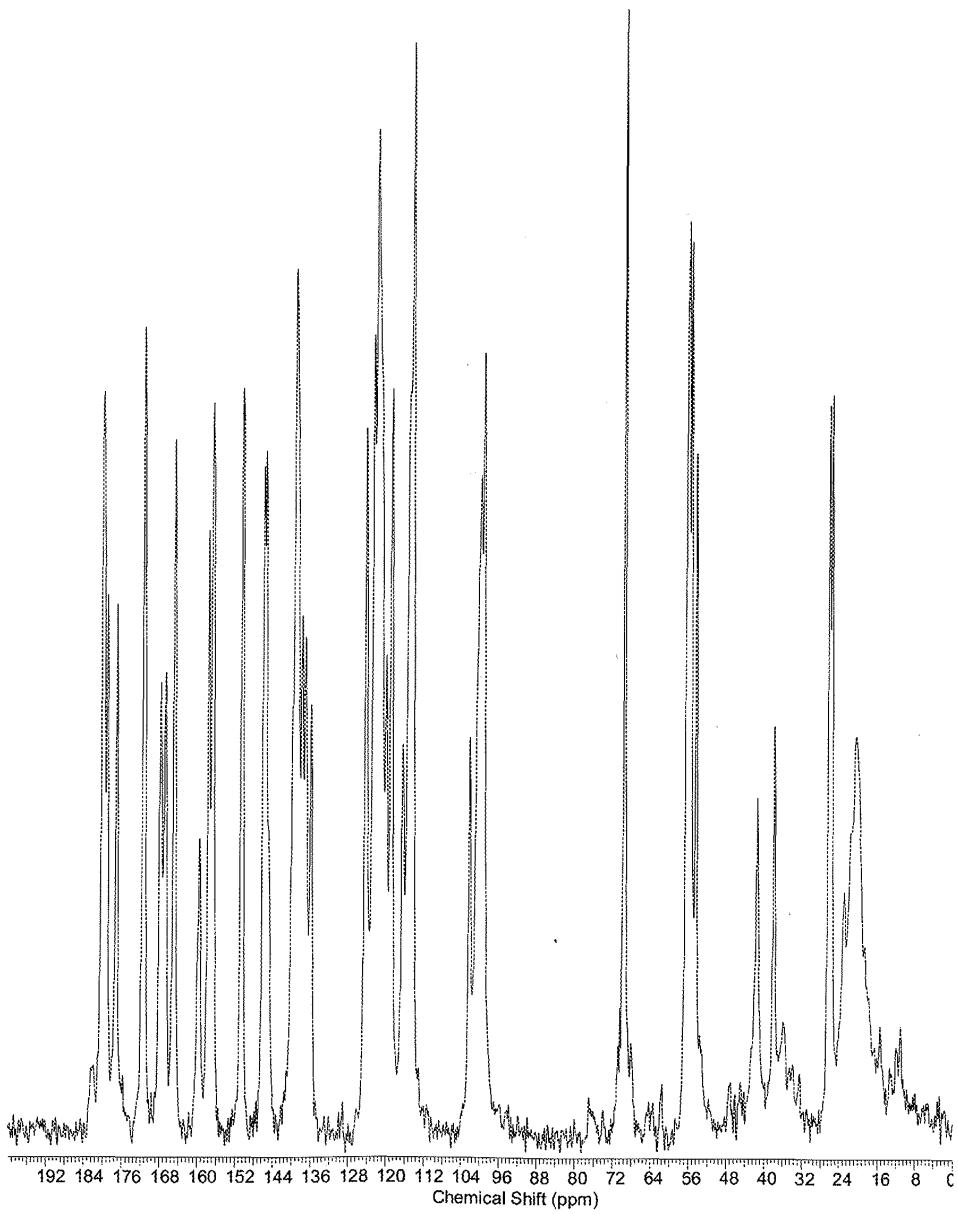
EXEL2_00132144

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Appx204

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Figure 9



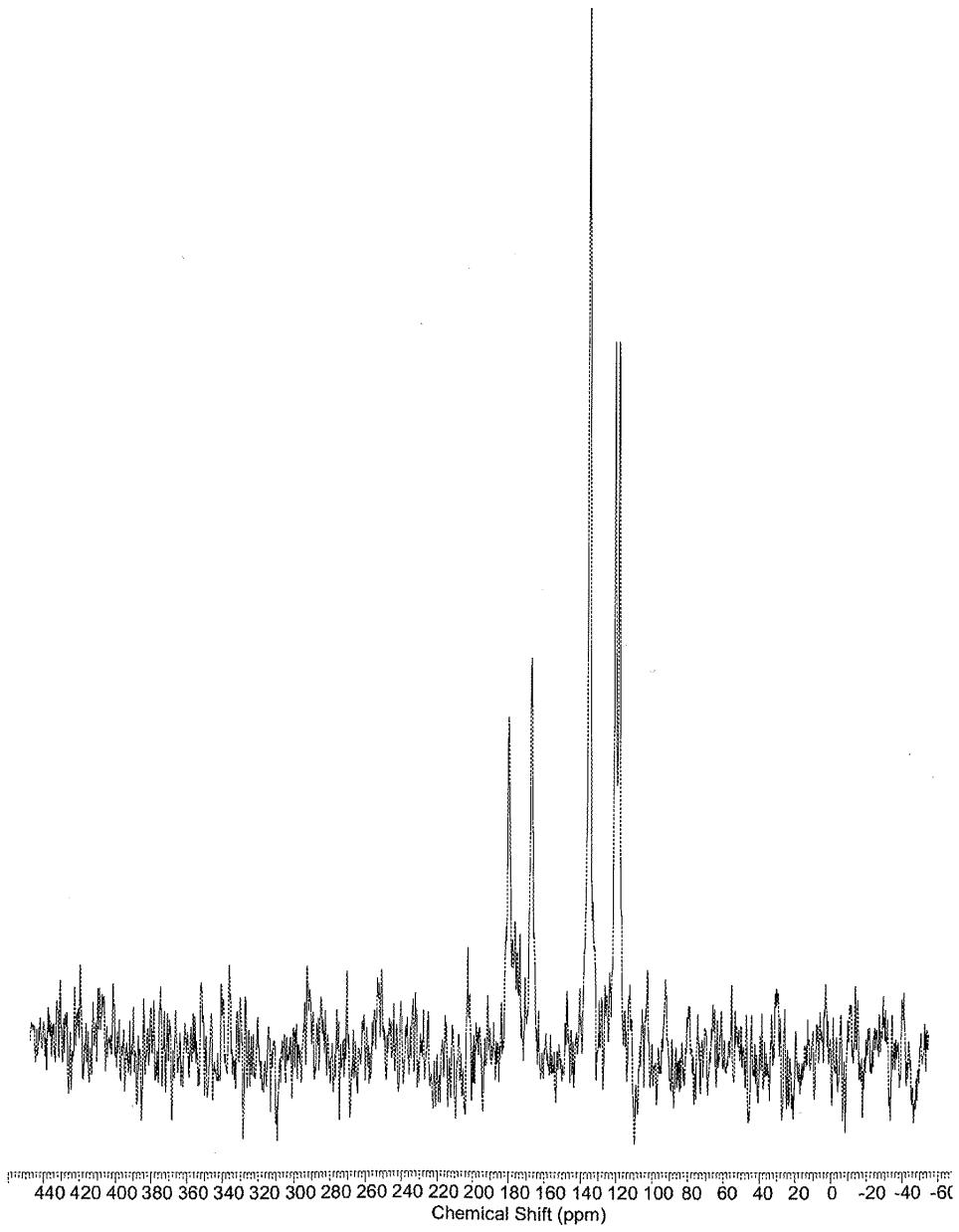
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Appx205

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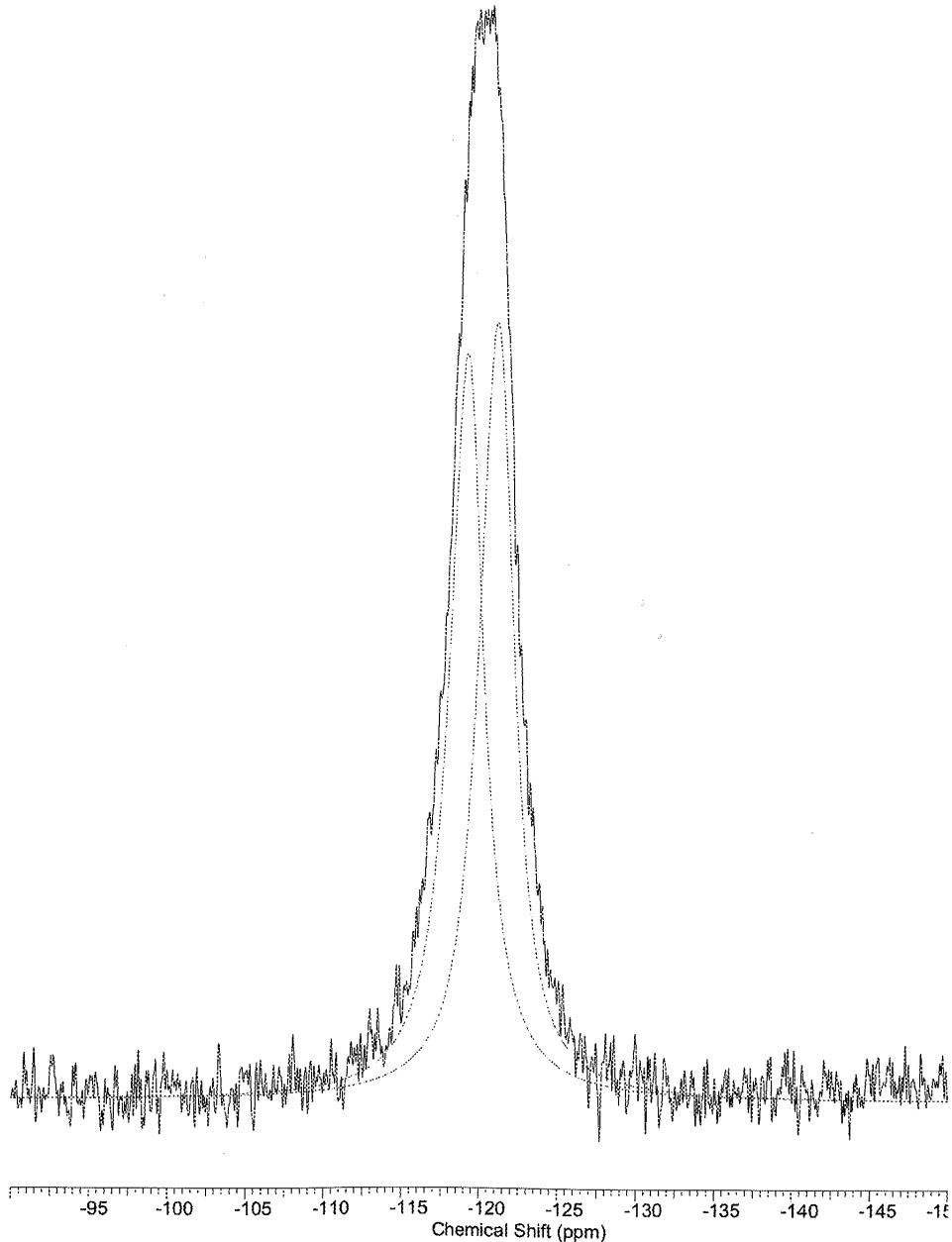
Figure 10



EXEL2_00132146

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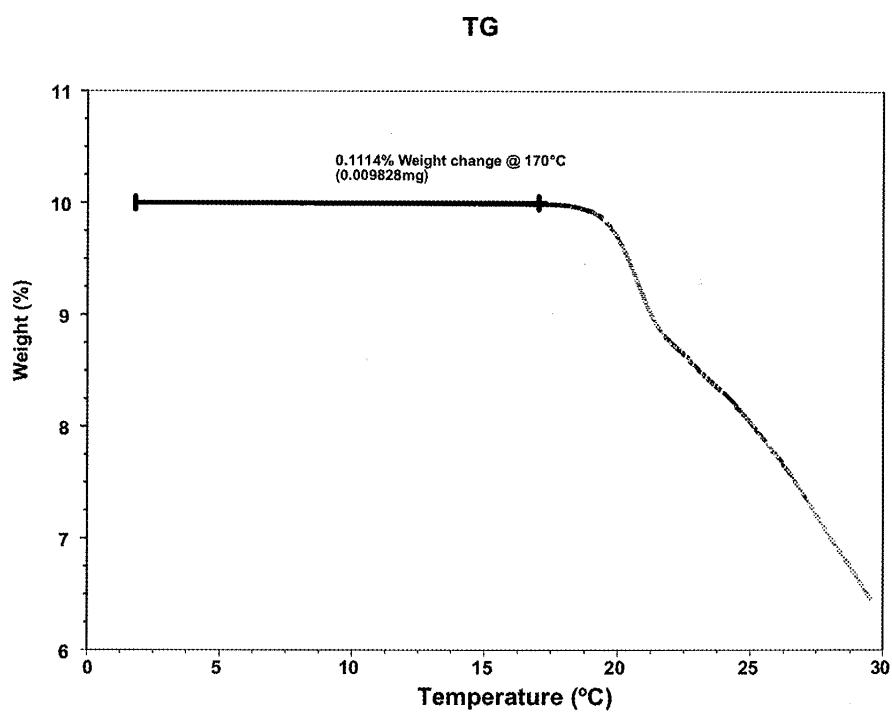
Figure 11



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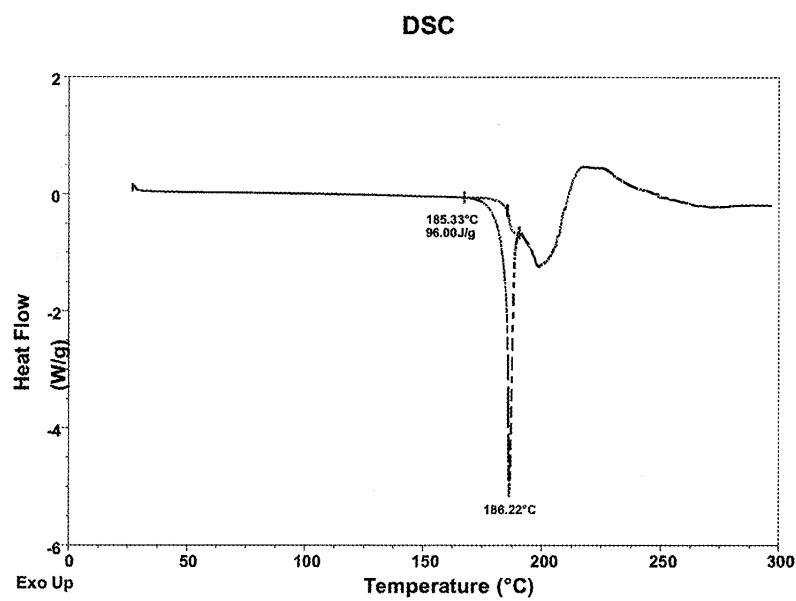
Figure 12



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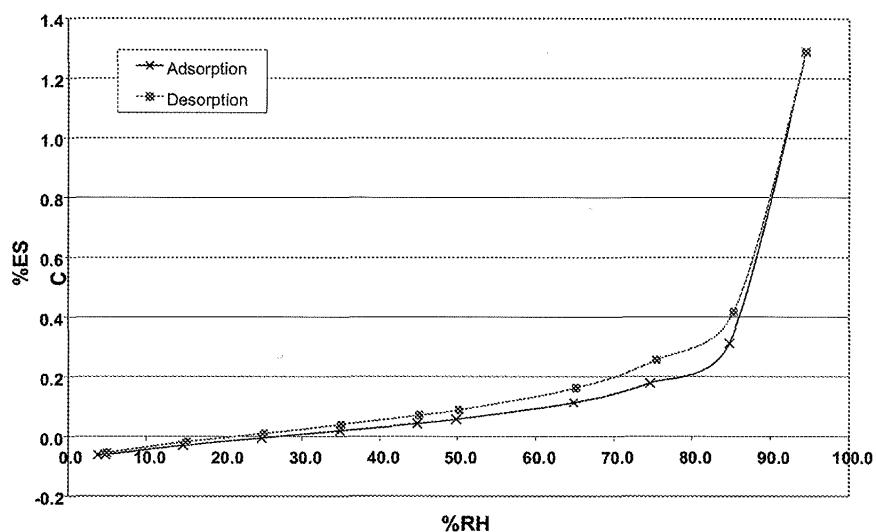
Figure 13



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Figure 14



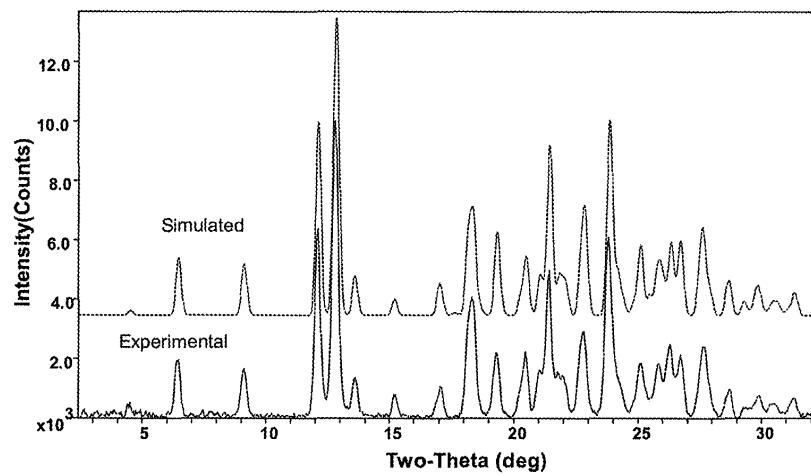
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Appx210

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Figure 15



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Appx211

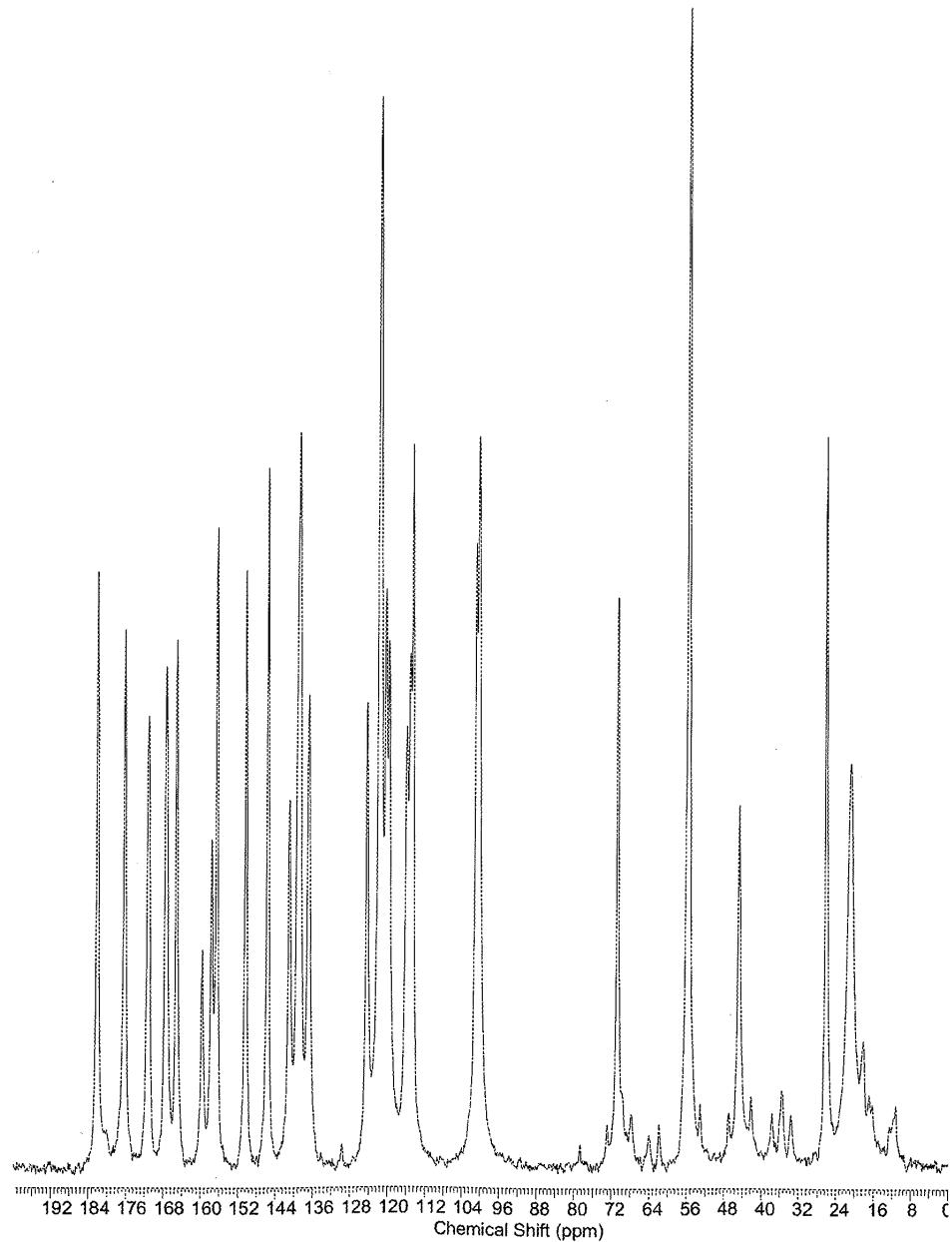
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Figure 16



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Appx212

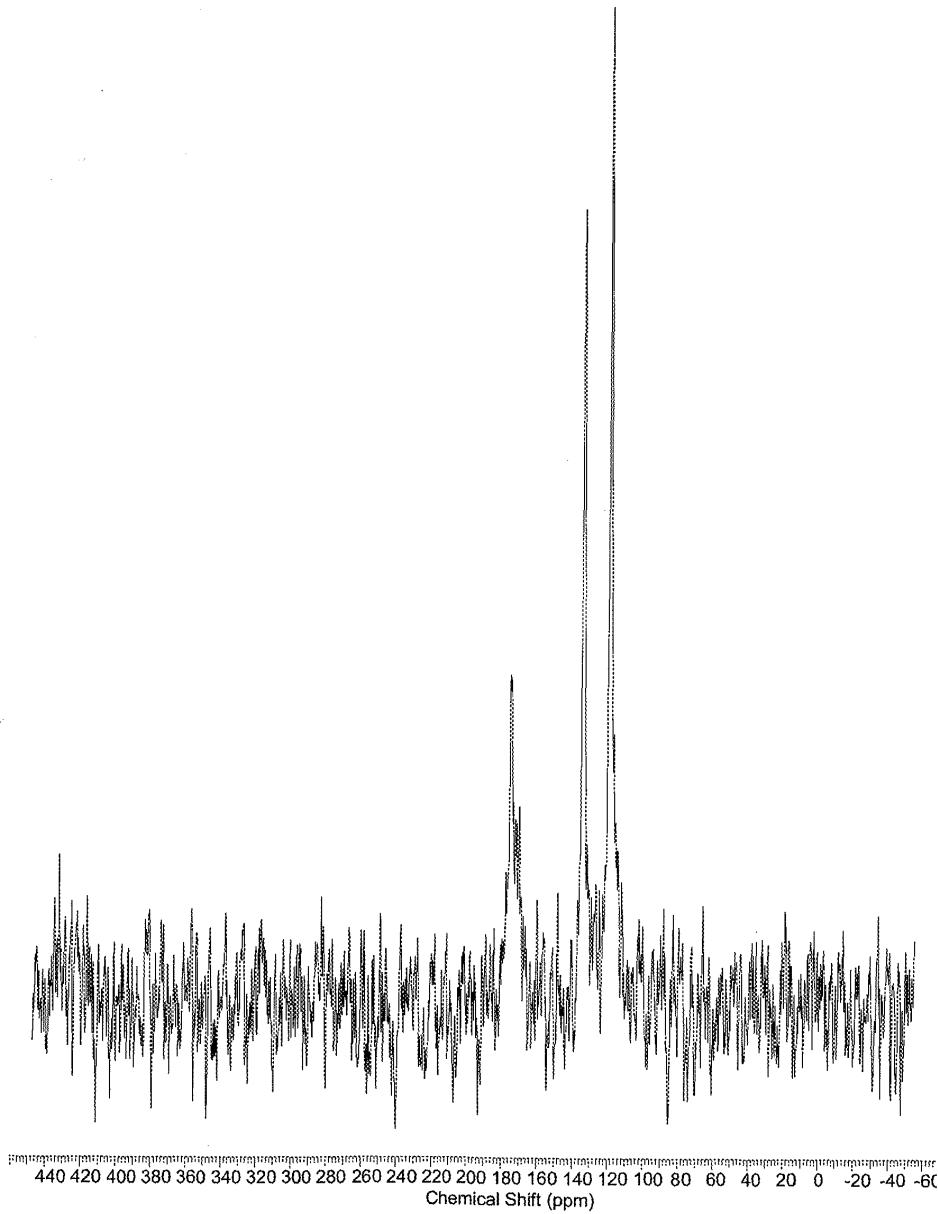
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Figure 17



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Appx213

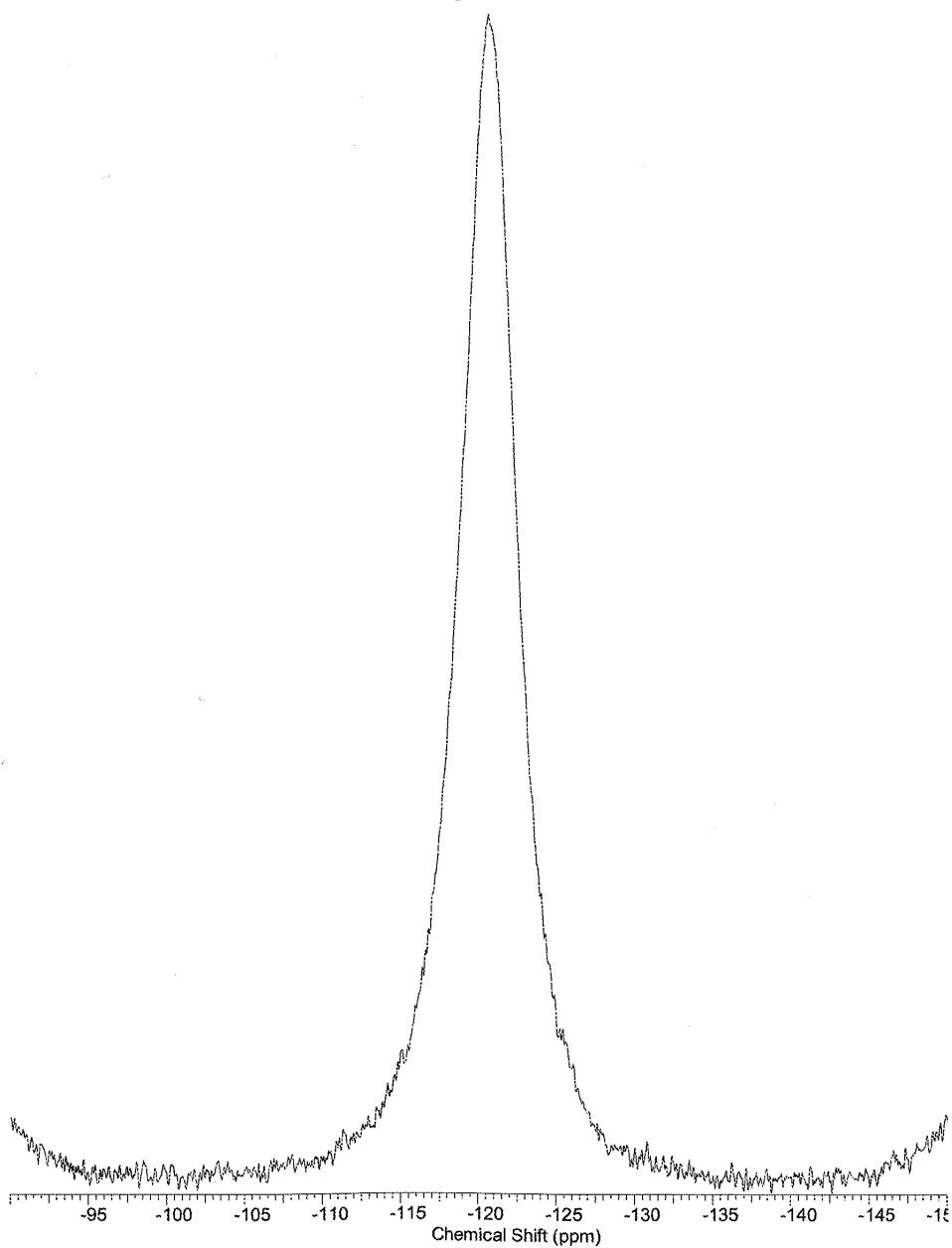
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Figure 18



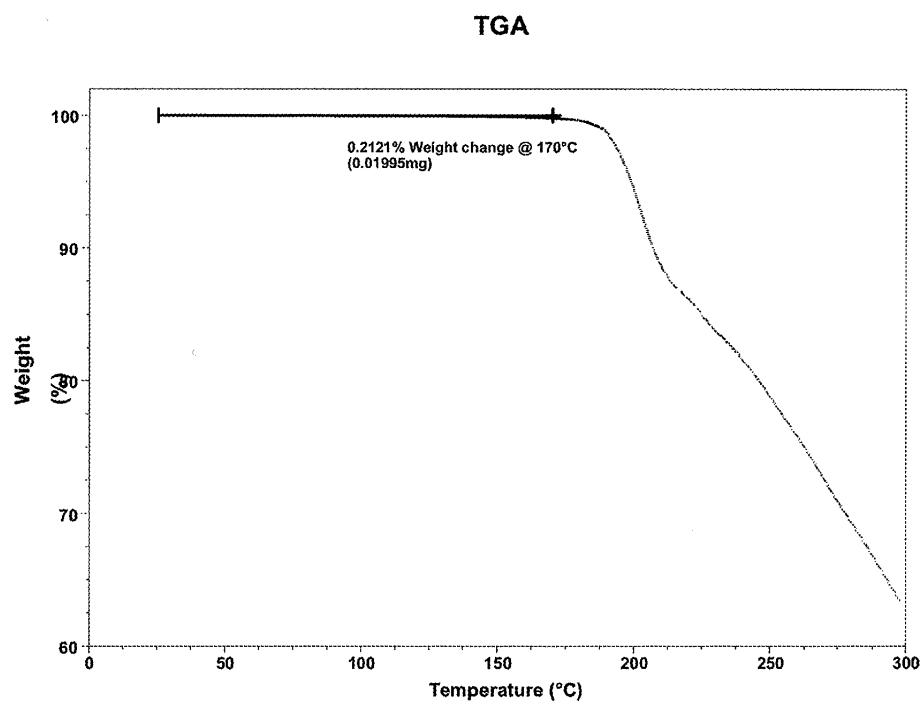
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Appx214

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Figure 19



EXEL2_00132155

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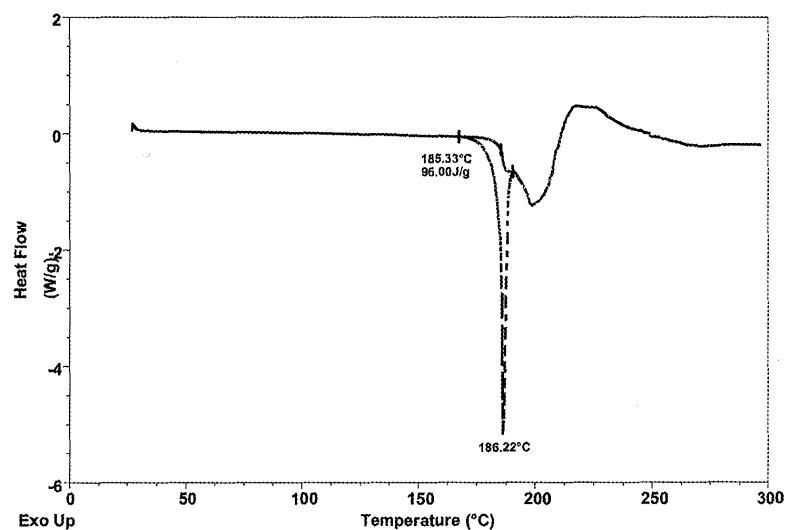
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Figure 20

DSC



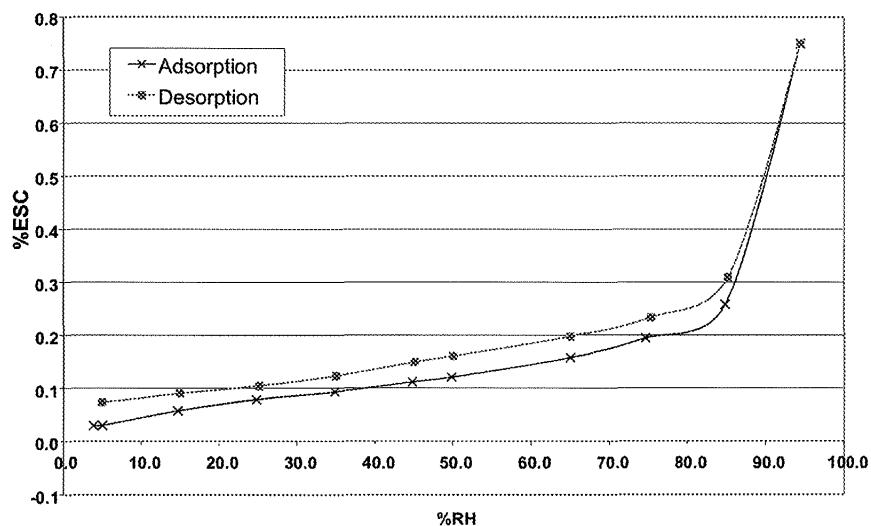
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Appx216

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Figure 21



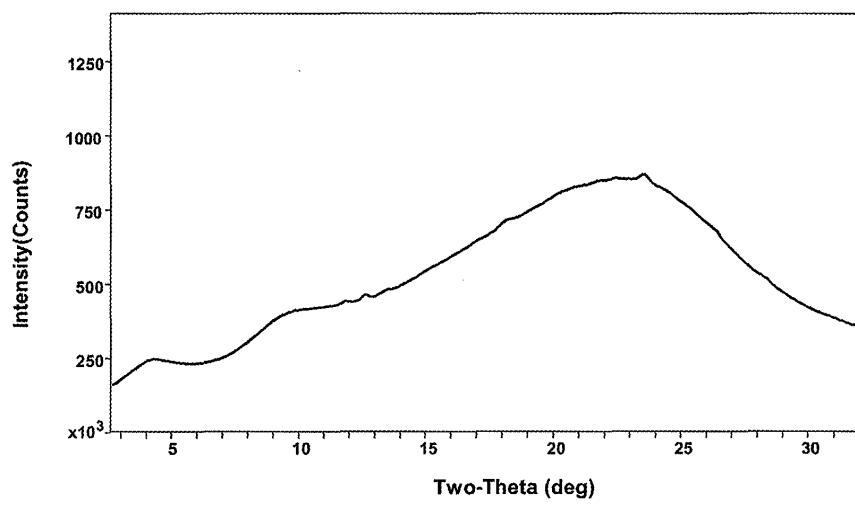
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Appx217

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Figure 22



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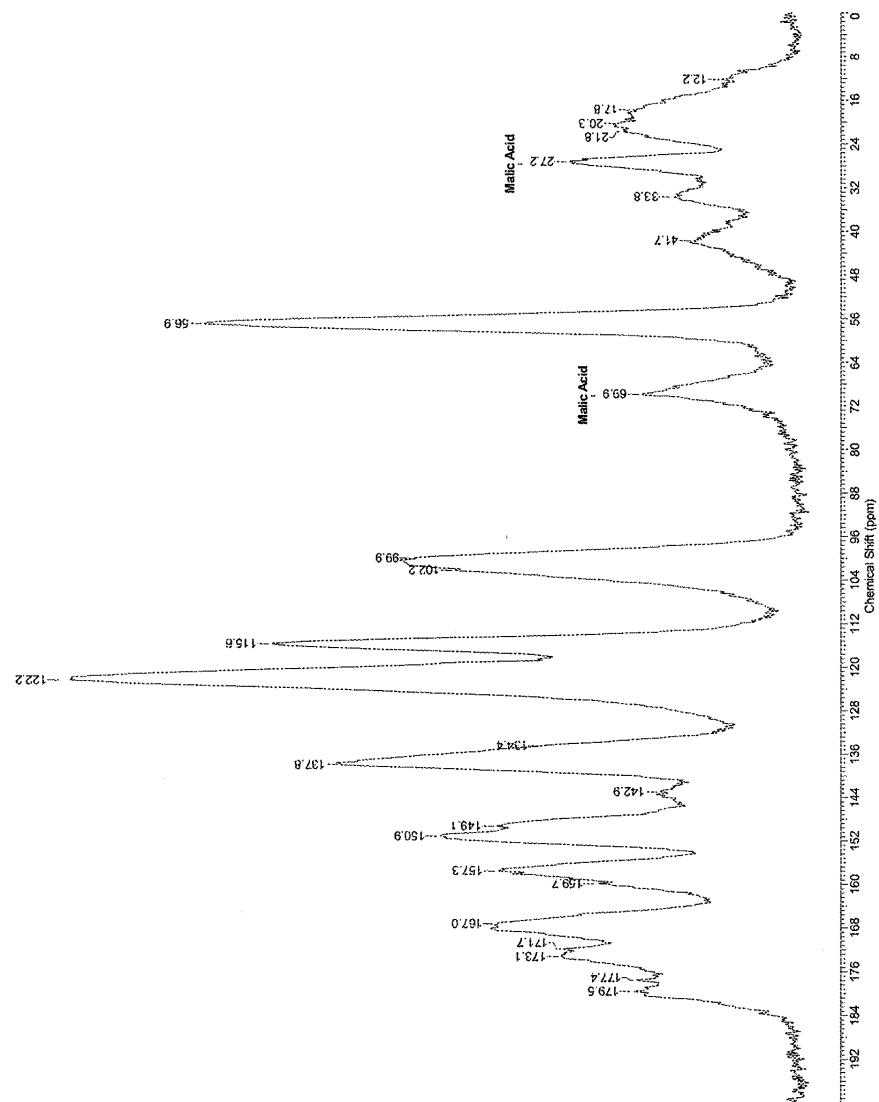
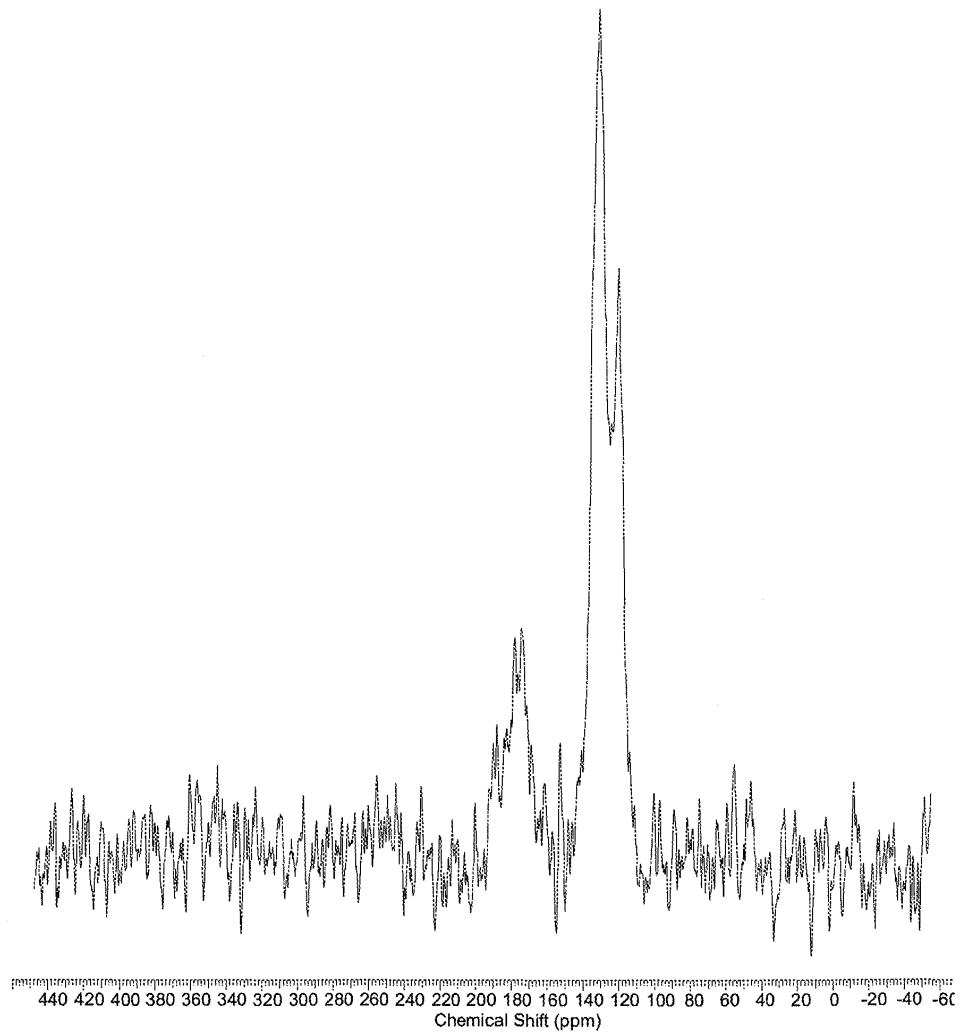


Figure 23

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Figure 24



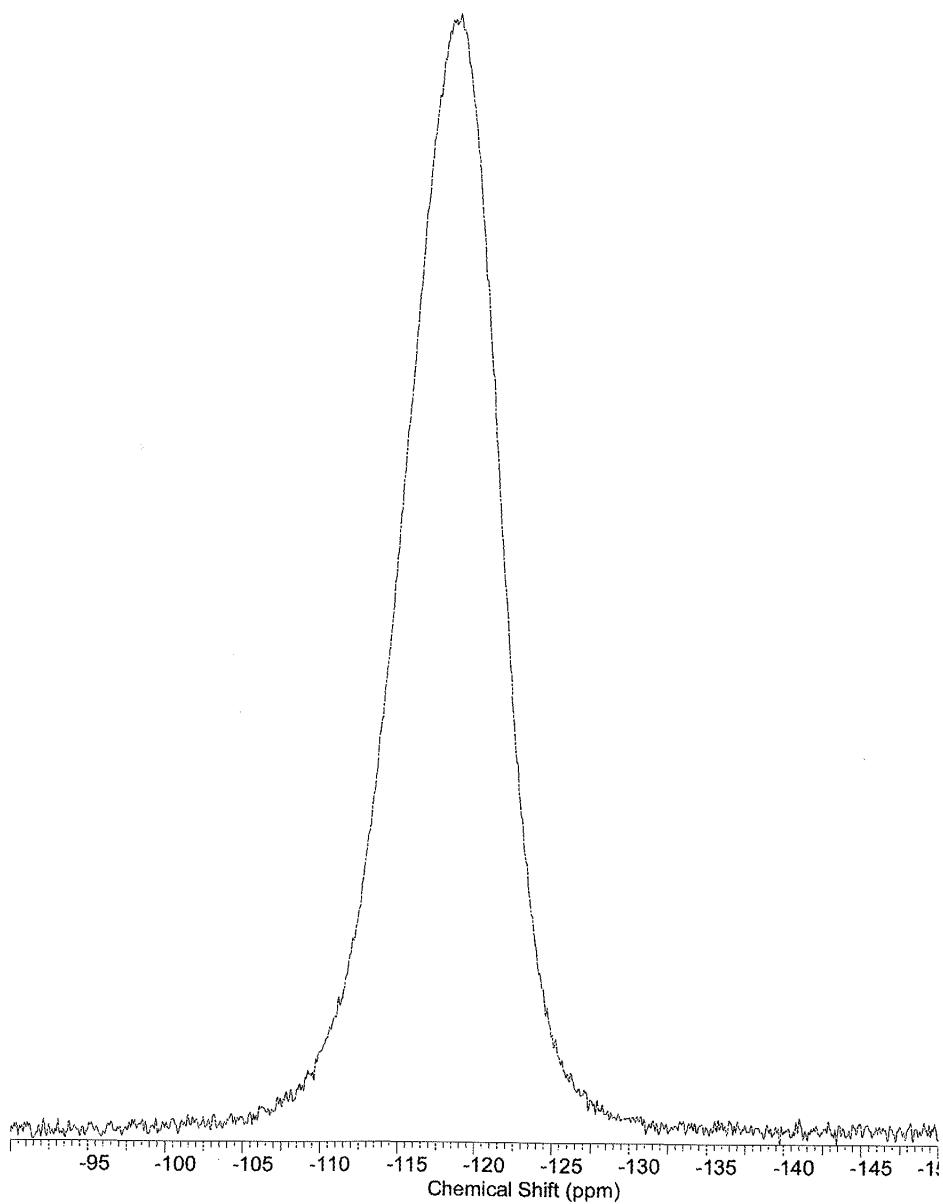
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Figure 25



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Appx221

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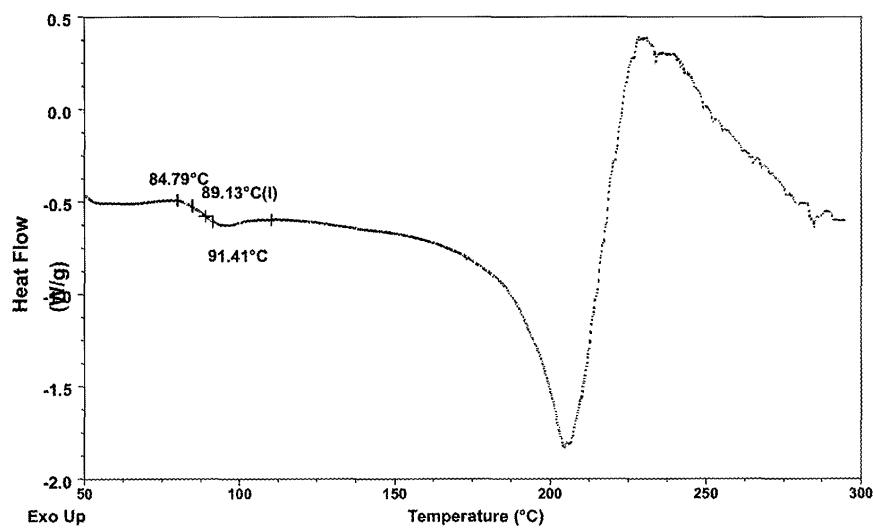
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Figure 26

DSC



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Appx222

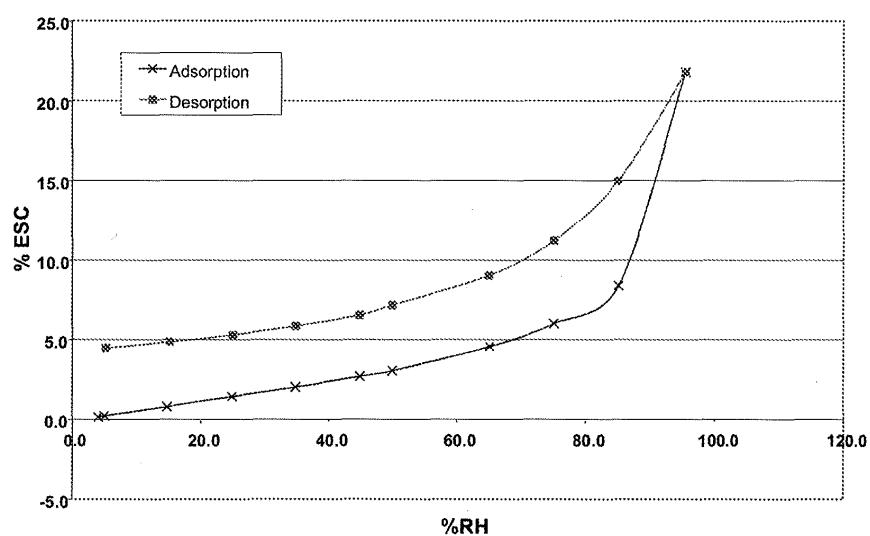
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Figure 27



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Appx223

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**MALATE SALT OF
N-(4-[6,7-BIS(METHYLOXY)
QUINOLIN-4-YL]OXY)PHENYL)-N'-(4-
FLUOROPHENYL)CYCLOPROPANE-1,1-
DICARBOXAMIDE, AND CRYSTALLINE
FORMS THEREOF FOR THE TREATMENT
OF CANCER**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation application of U.S. Ser. No. 17/149,365, filed Jan. 14, 2021, which is a continuation application of U.S. Ser. No. 17/070,514, filed Oct. 14, 2020, which is a continuation application of U.S. Ser. No. 16/796, 250, filed Feb. 20, 2020, which is a continuation application of U.S. Ser. No. 15/617,725, filed Jun. 8, 2017, which is a division of U.S. Ser. No. 14/340,871, filed Jul. 25, 2014, which is a division of U.S. Ser. No. 13/145,054, filed Oct. 20, 2011, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2010/021194, filed Jan. 15, 2010, which claims the benefit of U.S. provisional application No. 61/145,421, filed Jan. 16, 2009, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to malate salts of N-(4-[6,7-bis(methyloxy)-quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and to crystalline and amorphous forms of the malate salts of N-(4-[6,7-bis(methyloxy)-quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. The malate salts of N-(4-[6,7-bis(methyloxy)-quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide include one of (1) the (L)-malate salt, (2) the (D)-malate salt, (3) the (D,L)-malate salt, and (4) mixtures thereof. The disclosure also relates to pharmaceutical compositions comprising at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

The disclosure also relates to pharmaceutical compositions comprising a crystalline or an amorphous form of at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure also relates to methods of treating cancer comprising administering at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure further relates to methods of treating cancer comprising administering a crystalline or an amorphous form of at least one malate salt of N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

BACKGROUND

Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example,

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thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., *DN&P* 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis in vivo (See: Maulik et al *Cytokine & Growth Factor Reviews* 2002 13, 41-59). c-Met, VEGFR2 and/or Ret overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components). The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and convert it into an oncogene product.

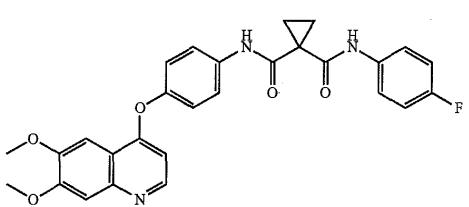
Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc. Technol.* 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both vascular endothelial growth factor (VEGF) receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc. Technol.* 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition.

Accordingly, small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including Ret, c-Met and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is N-(4-[6,7-bis(methyloxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, which has the chemical structure:

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WO 2005/030140 describes the synthesis of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{(4-fluorophenyl)cyclopropane-1,1-dicarboxamide} (Example 12, 37, 38, and 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases, (Assays, Table 4, entry 289). Example 48 is on paragraph [0353] in WO 2005/030140.

Besides therapeutic efficacy, the drug developer endeavors to provide a suitable form of the therapeutic agent that has properties relating to processing, manufacturing, storage stability, and/or usefulness as a drug. Accordingly, the discovery of a form that possesses some or all of these desired properties is vital to drug development.

Applicants have found a salt form of the drug N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{(4-fluorophenyl)cyclopropane-1,1-dicarboxamide} that has suitable properties for use in a pharmaceutical composition for the treatment of a proliferative disease such as cancer. The novel salt form of the invention exists in crystalline and amorphous forms

SUMMARY

This disclosure relates to malate salts of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{(4-fluorophenyl)cyclopropane-1,1-dicarboxamide} as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

Another aspect relates to crystalline and amorphous forms of the malate salts of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{(4-fluorophenyl)cyclopropane-1,1-dicarboxamide} as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the experimental XRPD pattern for crystalline Compound (I), Form N-1 at 25° C.

FIG. 2 shows the solid state ¹³C NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 3 shows the solid state ¹⁵N NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 4 shows the solid state ¹⁹F NMR spectrum of crystalline Compound (I), Form N-1.

FIG. 5 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-1.

FIG. 6 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-1.

FIG. 7 shows the moisture sorption of crystalline Compound (I), Form N-1.

FIG. 8 shows the experimental XRPD pattern for crystalline Compound (I), Form N-2 at 25° C.

FIG. 9 shows the solid state ¹³C NMR spectrum of crystalline Compound (I), Form N-2.

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FIG. 10 shows the solid state ¹⁵N NMR spectrum of crystalline Compound (I), Form N-2.

FIG. 11 shows the solid state ¹⁹F NMR spectrum of crystalline Compound (I), Form N-2.

FIG. 12 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-2.

FIG. 13 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-2.

FIG. 14 shows the moisture sorption of crystalline Compound (I), Form N-2.

FIG. 15 shows the experimental and simulated XRPD patterns for crystalline Compound (III), Form N-1 at room temperature.

FIG. 16 shows the solid state ¹³C NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 17 shows the solid state ¹⁵N NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 18 shows the solid state ¹⁹F NMR spectrum of crystalline Compound (III), Form N-1.

FIG. 19 shows the thermal gravimetric analysis (TGA) of crystalline Compound (III), Form N-1.

FIG. 20 shows the differential scanning calorimetry (DSC) of crystalline Compound (III), Form N-1.

FIG. 21 shows the moisture sorption of crystalline Compound (III), Form N-1.

FIG. 22 shows the XRPD pattern of amorphous Compound (I) at room temperature.

FIG. 23 shows the solid state ¹³C NMR spectrum of amorphous Compound (I).

FIG. 24 shows the solid state ¹⁵N NMR spectrum of amorphous Compound (I).

FIG. 25 shows the solid state ¹⁹F NMR spectrum of amorphous Compound (I).

FIG. 26 shows the differential scanning calorimetry (DSC) of amorphous Compound (I).

FIG. 27 shows the moisture sorption of amorphous Compound (I).

DETAILED DESCRIPTION

This disclosure relates to improvements of the physicochemical properties of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{(4-fluorophenyl)cyclopropane-1,1-dicarboxamide}, whereby this compound may be suitable for drug development. Disclosed herein are malate salts of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{(4-fluorophenyl)cyclopropane-1,1-dicarboxamide}. New solid state forms of those salts are also disclosed. The malate salts as well as their crystalline and amorphous forms disclosed herein each represent separate aspects of the disclosure. Although the malate salts and their solid state forms are described herein, the invention also relates to novel compositions containing the disclosed salts and solid state forms. Therapeutic uses of the salts and solid state forms described as well as therapeutic compositions containing them represent separate aspects of the disclosure. The techniques used to characterize the salts and their solid state forms are described in the examples below. These techniques, alone or in combination, may be used to characterize the salts and their solid state forms disclosed herein. The salts and their solid state forms may be also characterized by reference to the disclosed figures.

N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-{(4-fluorophenyl)cyclopropane-1,1-dicarboxamide} was found to have an enzyme Ret IC₅₀ value of about 5.2 nM (nanomolar) and an enzyme c-Met IC₅₀ value of about 1.3

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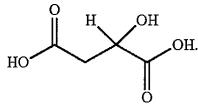
nM (nanomolar). The assay that was used to measure this c-Met activity is described in paragraph [0458] in WO2005-030140.

RET biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described in WO2005-030140. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 2 μ M ATP, 1 μ M poly-EY and 15 nM RET (baculovirus expressed human RET kinase domain M700-D1042 with a (His)₆ tag on the N-terminus) in a 20 μ L assay buffer (20 mM Tris-HCl pH 7.5, 10 mM MgCl₂, 0.01% Triton X-100, 1 mM DTT, 3 mM MnCl₂). The mixture was incubated at ambient temperature for 2 hours after which 20 μ L luciferase-luciferin mix was added and the chemiluminescent signal read using a Wallac Victor² reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5 μ g/mL oxalic acid (pH 7.8), 5 mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μ M AMP, 28 μ g/mL luciferin and 40,000 units of light/mL luciferase.

Malate Salts of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

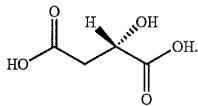
This disclosure relates to malate salts of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. These malate salts are a combination of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide with malic acid which forms a 1:1 malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Malic acid has the following structure:



Due to its chiral carbon, two enantiomers of malic acid exist, (L)-malic acid and (D)-malic acid.

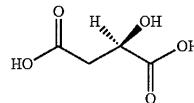
(L)-malic acid has the following structure:



There are various names or designations for the (L)-malic acid that are known in the art. These include butanedioic acid, hydroxy-, (2S)-(9CI); butanedioic acid, hydroxy-, (S)-; malic acid, L-(8CI); malic acid, 1-(3CI); (-)-(S)-malic acid; (-)-Hydroxysuccinic acid; (-)-(L)-malic acid; (-)-malic acid; (2S)-2-hydroxybutanedioic acid; (2S)-2-hydroxysuccinic acid; (S)-malic acid; apple acid; L-(-)-malic acid; (L)-malic acid; NSC 9232; S-(-)-malic acid; and S-2-hydroxybutanedioic acid.

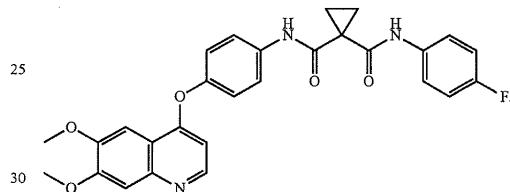
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(D) malic acid has the following structure:



There are various names or designations for the (D)-malic acid that are known in the art. These include butanedioic acid, 2-hydroxy-, (2R)-, butanedioic acid, hydroxy-, (2R)-(9CI); butanedioic acid, hydroxy-, (R)-; (+)-malic acid; (2R)-2-hydroxybutanedioic acid; (2R)-malic acid; (R)-(+)-malic acid; (R)-malic acid; D-(+)-2-hydroxysuccinic acid; D-(+)-malic acid; and D-malic acid.

As discussed above, the chemical structure of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is



There are no chiral carbons in its chemical structure. There are various names for N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide which are publicly known, and some of these various names or designations include 1,1-cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyloxy)phenyl]-N-(4-fluorophenyl)- and 1,1-cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyloxy)phenyl]-N-(4-fluorophenyl)-(9CI).

N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide can be prepared according to any of several different methodologies, either on a gram scale (<1 kg) or a kilogram scale (>1 kg). A gram-scale method is set forth in WO 2005-030140, which describes the synthesis of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Examples 25, 37, 38, and 48), which is hereby incorporated by reference. Alternatively, N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including the active compound(s), can be prepared on a kilogram scale using the procedure set forth in Example 1 below.

This disclosure relate to malate salts of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide: the (L)-malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound I); the (D)-malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound II); and the (DL)-malate salt of N-(4-{{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Compound III).

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Each has improved properties over N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and its other salts. The names used herein to characterize a specific form, e.g. "N-2" etc., are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics, but rather such names are used as mere identifiers that are to be interpreted in accordance with the characterization information presented herein.

The malate salts of N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, and particularly Compound (I), have a preferred combination of pharmaceutical properties for development. Under the conditions of 25° C./60% relative humidity (RH) and 40° C./60% RH, Compound (I) showed no change in assay, purity, moisture and dissolution. The DSC/TGA showed the Compound (I) to be stable up to 185° C. No solvent losses were observed. The uptake of water by the (L)-malate salt was reversible with a slight hysteresis. The amount of water taken up was calculated at about 0.60 wt % at 90% RH. The (L)-malate salt was synthesized with good yield and purity >90% and had sufficient solubility for use in a pharmaceutical composition. The amount of water associated with this salt was calculated at about 0.5 wt % by Karl Fischer analysis and correlates with TGA and GVS analysis. The (D)-malate salt of N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide will have the same properties as the (L)-malate salt of N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of the N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. For example, the hydrochloride salt of N-(4-[(6,7-bis(methoxy)quinolin-4-yl)oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide exhibits undesirable moisture sensitivity, changing phase upon exposure to high humidity (75% humidity) and high temperature (40° C.). The maleate salt had low solubility. The tartate salt had low crystallinity and low solubility. The phosphate salt exhibited an 8% weight gain due to absorption of H₂O—the highest among the salts tested.

The water solubility of the various salts was determined using 10 mg solids per mL water. The salts were prepared in a salt screen by reacting an acetone solution of the freebase with stock tetrahydrofuran (THF) solutions of a range of acids in about a 1:1 molar ratio. Table 1 below summarizes the water solubility and other data relating to the free base and each salt.

TABLE 1

	Solubility (mg/ml)
Free base	<<0.001 very low solubility
Propionate	<<0.001 no salt formation; mixture of free base and acid
Acetate	<<0.001 no salt formation; mixture of free base and acid
Succinate	0.010 no salt formation; mixture of free base and acid
Benzocate	0.005 no salt formation; mixture of free base and acid
L-Lactate	0.015 Amorphous, salt
Pyroglutamate	0.44 Amorphous, salt
Glycolate	0.016 Amorphous, salt
L-Ascorbate	0.053 low crystallinity
Sulfate	0.004 Crystalline salt, low solubility

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TABLE 1-continued

	Solubility (mg/ml)	
5 Tosylate	0.007	Crystalline salt, low solubility
Malonate	<<0.003	Crystalline salt, low solubility
2,5 dihydroxybenzoate	<<0.001	Crystalline Salt, low solubility
Fumarate	0.008	Crystalline Salt, low solubility
10 Citrate	0.002	Crystalline Salt, low solubility
Mesylate	0.175	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Esylate	0.194	Crystalline Salt; possible sulfonic acid formation when made with alcohol
15 Benzene-sulfonate	0.039	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Chloride	0.070	Crystalline but Hygroscopic; possible hydrate formation. Change in XRPD pattern upon exposure to humidity.
Maleate	0.005	Crystalline salt, possible hydrate formation; low solubility; different XRPD pattern observed upon scale up (possible polymorphism issue)
20 Phosphate	0.026	Crystalline but Hygroscopic.
L-Tartrate	0.014	Low degree of crystallinity; Hygroscopic.
(L)-Malate	0.059	Crystalline; non-Hygroscopic with no indication of hydrate formation. Suitable solubility, and chemical/physical stability.

Another aspect of this disclosure relates to crystalline forms of Compound (I), which include the N-1 and/or the N-2 crystalline form of Compound (I) as described herein. 30 Each of form of Compound (I) is a separate aspect of the disclosure. Similarly, another aspect of this disclosure relates to crystalline forms of Compound (II), which include the N-1 and/or the N-2 crystalline form of Compound (II) as described herein. Each of which is also a separate aspect of the disclosure. As is known in the art, the crystalline (D) malate salt will form the same crystalline form and have the same properties as crystalline Compound (I). See WO 2008/083319, which discusses the properties of crystalline enantiomers. Mixtures of the crystalline forms of Compounds (I) and (II) are another aspect of the disclosure.

The crystalline N-1 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

- (i) a solid state ¹³C NMR spectrum with peaks at 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1 ppm, ±0.2 ppm;
 - (ii) a solid state ¹³C NMR spectrum substantially in accordance with the pattern shown in FIG. 2;
 - (iii) an x-ray powder diffraction pattern (CuKα λ=1.5418 Å) comprising four or more peaks selected from: 6.4, 9.0, 12.0, 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6 °2θ±0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;
 - (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 1;
 - (v) a solid state ¹⁵N NMR spectrum with peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ±0.2 ppm; and/or
 - (vi) a solid state ¹⁵N NMR spectrum substantially in accordance with the pattern shown in FIG. 3.
- Other solid state properties which may be used to characterize the crystalline N-1 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below. For crystalline Compound (I), the solid state phase and the degree of crystallinity remained unchanged after exposure to 75% RH at 40° C. for 1 week.

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The crystalline N-2 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

- (i) a solid state ^{13}C NMR spectrum with peaks at 23.0, 25.9, 38.0, 54.4, 56.11, 41.7, 69.7, 102.0, 122.5, 177.3, 25.9.3, 180.0, and 180.3, ± 0.2 ppm;
- (ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. 9;
- (iii) an x-ray powder diffraction pattern ($\text{CuK}\alpha \lambda=1.5418 \text{\AA}$) comprising four or more peaks selected from: 6.4, 9.1, 12.0, 12.8, 13.7, 17.1, 20.9, 21.9, 22.6, and 23.7 $^{\circ}2\theta \pm 0.2$, wherein measurement of the crystalline form is at an ambient room temperature;
- (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 8;
- (v) a solid state ^{15}N NMR spectrum with peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm; and/or
- (vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. 10.

Other solid state properties which may be used to characterize the crystalline N-2 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below.

In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-1 form.

In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-2 form.

The disclosure also relates to amorphous forms of Compounds (I) and (II). The preparation and solid state properties and characteristics of the amorphous form of Compound (I) are described in the examples below. The amorphous forms of Compounds (I) and (II) represent another aspect of the disclosure.

One further aspect of the disclosure relates to mixtures of Compound (I) and Compound (II). The mixtures may have from greater than zero weight % to less than 100 weight % Compound (I) and from less than 100 weight % to greater than zero weight % Compound (II), based on the total weight of Compound (I) and Compound (II). In other embodiments, the mixture comprises from about 1 to about 99 weight % Compound (I) and from about 99 to about 1 weight % Compound (II), based on the total weight of Compound (I) and Compound (II) in said mixture. In a further embodiment, the mixture comprises from about 90 weight % to less than 100 weight % Compound (I) and from greater than zero weight % to about 10 weight % Compound (II), based on the total weight of Compound (I) and Compound (II). Accordingly, the mixture may have 1-10% by weight of Compound (I); 11-20% by weight of Compound (I); 21-30% by weight of Compound (I); 31-40% by weight of Compound (I); 41-50% by weight of Compound (I); 51-60% by weight of Compound (I); 61-70% by weight of Compound (I); 71-80% by weight of Compound (I); 81-90% by weight of Compound (I); or 91-99% by weight of Compound (I) with the remaining weight percentage of malate salt being that of Compound (II).

Another aspect of this disclosure relates to crystalline forms of (DL)-malate salt of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, Compound (III). The (DL)-malate salt is prepared from racemic malic acid. The crystalline N-1

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form of Compound (III) as described here may be characterized by at least one of the following:

- (i) a solid state ^{13}C NMR spectrum with four or more peaks selected from 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, 182.1 ppm, ± 0.2 ppm;
- (ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. 16;
- (iii) a powder x-ray diffraction pattern ($\text{CuK}\alpha \lambda=1.5418 \text{\AA}$) comprising four or more 2 θ values selected from: 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6, ± 0.2 $^{\circ}2\theta$, wherein measurement of the crystalline form is at temperature of room temperature;
- (iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. 15;
- (v) a solid state ^{15}N NMR spectrum with peaks at 119.6, 134.7, and 175.5 ppm, ± 0.2 ppm; and/or
- (vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. 17.

Other solid state properties which may be used to characterize the crystalline N-1 form of Compound (III) are shown in the figures and discussed in the examples below. In one embodiment, the N-1 Form of Compound (III) is characterized by unit cell parameters approximately equal to the following:

Cell dimensions: $a=14.60 \text{\AA}$

$b=5.20 \text{\AA}$

$c=39.09 \text{\AA}$

$\alpha=90.0^\circ$

$\beta=90.4^\circ$

$\gamma=90.0^\circ$

Space group: $P2_1/n$

Molecules of Compound (I)/unit cell: 4

Volume= 2969\AA^3

Density (calculated)= 1.422 g/cm^3

The unit cell parameters of Form N-1 of Compound (III) were measured at a temperature of approximately 25°C , e.g., ambient or room temperature.

Each of the N-1 and N-2 crystalline forms of Compounds (I) and (II) and the crystalline form N-1 of Compound (III) have unique characteristics that can distinguish them one from another. These characteristics can be understood by comparing the physical properties of the solid state forms which are presented in the Examples below. For example, Table 2 lists characteristic XRPD peak positions ($^{\circ}2\theta \pm 0.2$) for crystalline Compound (III), Form N-1 and Forms N-1 and N-2 of crystalline Compound (I). Amorphous forms do not display reflection peaks in their XRPD patterns.

TABLE 2

Characteristic diffraction peak positions (degrees $2\theta \pm 0.2$) @ RT, based on pattern collected with a diffractometer ($\text{CuK}\alpha$) with a spinning capillary.		
Compound (I) Form N-1	Compound (I) Form N-2	Compound (III) Form N-1
6.4	6.4	6.4
9.0	9.1	9.1
12.0	12.0	12.1
12.8	12.8	12.8
13.5	13.7	13.6
16.9	17.1	17.1
19.4*	20.9*	19.3
21.5*	21.9*	21.4
22.8*	22.6	22.8

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TABLE 2-continued

Characteristic diffraction peak positions (degrees $2\theta \pm 0.2$) @ RT, based on pattern collected with a diffractometer ($\text{CuK}\alpha$) with a spinning capillary.		
Compound (I) Form N-1	Compound (I) Form N-2	Compound (III) Form N-1
25.1*	23.7	25.1
27.6*	—	27.6

*unique reflections between Compound (I), Form N-1 and Compound (I), Form N-2.

The unique reflections between Forms N-1 and N-2 of crystalline Compound (II) are designated by an asterisk (*). As discussed above, Compound (II) is an enantiomer of Compound (I) and thus, Compound (II), Form N-1 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-1. Likewise, Compound (II), Form N-2 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-2. Compounds (I) and (II) are distinct from one another based on their absolute stereochemistry, i.e., the (L)-malate salt versus the (D)-malate salt, respectively. Crystalline Compound (III), Form N-1, is distinct as the (D,L)-malate salt.

The characteristic peaks from the solid state NMR may also serve to distinguish the crystalline and amorphous forms disclosed herein. For example, Table 3 lists characteristic solid state ^{13}C NMR peaks for crystalline Compound (III), Form N-1; crystalline Compound (I). Forms N-1 and N-2, and the amorphous form of Compound (I).

TABLE 3

Solid State Carbon-13 NMR Resonances (ppm, ± 0.2 ppm)			
(I) Form N-1	(I), Form N-2	(III), Form N-1	(I), Amorphous
18.1	23.0	20.8	27.2
42.9	25.9	26.2	33.8
44.5	38.0	44.8	142.9
54.4	54.4	70.7	—
56.1	56.1	114.7	—
70.4	41.7	141.1	—
123.2	69.7	145.7	—
156.2	102.0	176.3	—
170.8	122.5	182.1	—
175.7	177.3	—	—
182.1	179.3	—	—
—	180.0	—	—
—	180.3	—	—

The solid state ^{19}F and ^{15}N NMR spectra, discussed below, provide data for similar comparison and characterization. As discussed above, being an enantiomer of Compound (I), crystalline Forms N-1 and N-2 and the amorphous form of Compound (II) will have the same solid state NMR resonances, and unique peaks between them, as those listed in Table 3 for Forms N-1 and N-2 of crystalline Compound (I). Pharmaceutical Compositions and Methods of Treatment

Another aspect of this disclosure relates to a pharmaceutical composition comprising at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient. The amount of Compound (I), Compound (II), Compound (III), or the combinations thereof in the pharmaceutical composition can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may individually be present in the pharmaceutical composition as one of the solid state forms discussed above or combinations thereof. The crys-

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talline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a solid or dispersion pharmaceutical composition comprising at least one of a therapeutically effective amount of a crystalline form of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient.

Another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms, with crystalline Compound (I), Form N-1 or N-2 being preferred. Accordingly another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, the method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer (including astrocytic tumor, which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components), lung cancer (including non-small cell lung cancer), bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, lymphoma, solid tumors, Hodgkin's disease, non-Hodgkin's lymphoma or thyroid cancer thyroid cancer (including medullary thyroid cancer).

Tyrosine kinase inhibitors have also been used to treat non-small cell lung cancer (NSCLC). Gefitinib and erlotinib are angiogenesis inhibitors that target receptors of an epidermal growth factor called tyrosine kinase. Erlotinib and Gefitinib are currently being used for treating NSCLC. Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-[{6,7-bis(methoxy)quinolin-4-yl}oxy]-phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof, optionally in combination with Erlotinib or Gefitinib. In another embodiment, the combination is with Erlotinib.

Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating a method of treating non-small cell lung cancer

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(NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. In another embodiment, the combination administered in this method is Erlotinib with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof.

Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating an astrocytic tumor comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof. The amount administered can be a therapeutically effective amount.

Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating thyroid cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In

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another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms.

Accordingly another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, a crystalline form of Compound (I), Compound (II), or any combination of Compound (I) and (II). The amount of Compound (I), Compound (II), or any combination of Compound (I) and (II) administered can be a therapeutically effective amount.

Another aspect of this disclosure relates to a use of the N-(4-[6,7-bis(methoxy)quinolin-4-yl]oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate salt according to any of the above embodiments for the manufacture of a medicament for the treatment of a disease or disorder discussed above. When dissolved, a crystalline or amorphous form according to this disclosure loses its solid state structure, and is therefore referred to as a solution of, for example, Compound (I). At least one crystalline form disclosed herein may be used to prepare at least one liquid formulation in which at least one crystalline form according to the disclosure is dissolved and/or suspended.

A pharmaceutical composition such as discussed above may be any pharmaceutical form which contains active Compound (I), Compound (II) and/or Compound (III), including the solid state forms thereof (hereinafter referred to as active compound(s)). The pharmaceutical composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. The pharmaceutical compositions generally contain about 1% to about 99% by weight of the active compound(s), or a crystalline form of the active compound(s), and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of active compound, with the rest being suitable pharmaceutical excipients or other adjuvants, as discussed below.

A "therapeutically effective amount of the active compounds, or a crystalline or amorphous form of the active compound(s), according to this disclosure to inhibit, regulate and/or modulate the signal transduction of kinases (discussed here concerning the pharmaceutical compositions)

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refers to an amount sufficient to treat a patient suffering from any of a variety of cancers associated with abnormal cell proliferation and angiogenesis. A therapeutically effective amount according to this disclosure is an amount therapeutically useful for the treatment or prevention of the disease states and disorders discussed herein. Compounds (I), (II), and/or (III) (including their solid state forms), possess therapeutic activity to inhibit, regulate and/or modulate the signal transduction of kinases such as described in WO2005-030140. N-(4-[(6,7-bis(methoxy)quinolin-4-yl] 10
oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The actual amount required for treatment of any particular patient will depend upon a variety of factors including the disease state being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex and diet of the patient; the mode of administration; the time of administration; the route of administration; and the rate of excretion of the active compound(s), or a crystalline form of the active compound(s), according to this disclosure; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J. Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference. The active compound(s), or a crystalline form of active compound(s), according to this disclosure and pharmaceutical compositions comprising them, may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. They may also be co-formulated with one or more of such agents in a single pharmaceutical composition.

Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends partly upon the desired method of administration to be used. For a pharmaceutical composition of this disclosure, that is, one of the active compound(s), or a crystalline form of the active compound(s), of this disclosure, a carrier should be chosen so as to substantially maintain the particular form of the active compound(s), whether it would be crystalline or not. In other words, the carrier should not substantially alter the form the active compound(s) are. Nor should the carrier be otherwise incompatible with the form of the active compound(s), such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

The pharmaceutical compositions of this disclosure may be prepared by methods known in the pharmaceutical formulation art, for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). In a solid dosage forms Compound (I) is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for

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example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of this disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. If desired, a pharmaceutical composition of this disclosure may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and antioxidants, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, and butylated hydroxytoluene.

Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the active compound(s), or a crystalline form of the active compound(s), with, for example, suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

Because the active compound(s), or a crystalline form of the active compound(s), is maintained during their preparation, solid dosage forms are preferred for the pharmaceutical composition of this disclosure. Solid dosage forms for oral administration, which includes capsules, tablets, pills, powders, and granules, are particularly preferred. In such solid dosage forms, the active compound(s) mixed with at least one inert, pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier). Administration of the active compound(s), or a crystalline form of the active compound(s), in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravescically, intracisternally, or rectally, in the form of

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solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. One preferable route of administration is oral administration, using a convenient dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

General Preparation Methods of Crystalline Forms

Crystalline forms may be prepared by a variety of methods including, but not limited to, for example, crystallization or recrystallization from a suitable solvent mixture; sublimation; growth from a melt; solid state transformation from another phase; crystallization from a supercritical fluid; and jet spraying. Techniques for crystallization or recrystallization of crystalline forms of a solvent mixture include, but are not limited to, for example, evaporation of the solvent; decreasing the temperature of the solvent mixture; crystal seeding of a supersaturated solvent mixture of the compound and/or salt thereof; crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof; freeze drying the solvent mixture; and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S. R. Byrn, R. R. Pfeiffer, and J. G. Stowell, 2nd Edition, SSCI, West Lafayette, Ind. (1999).

In a crystallization technique in which solvent is employed, the solvent(s) are typically chosen based on one or more factors including, but not limited to, for example, solubility of the compound; crystallization technique utilized; and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution to which antisolvent is then added to decrease the solubility of the Compound (I) in the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

In one method that can be used in preparing crystals, Compound (I), Compound (II) and/or Compound (III) can be suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed Cooling Batch Crystallizers," J. W. Mullin and J. Nyvlt, Chemical Engineering Science, 1971, 26, 3690377. In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing large crystals, or by microcrystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

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A cooled crystallization mixture may be filtered under vacuum and the isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization solvent. After being washed, the product may be dried under a nitrogen purge to afford the desired crystalline form. The product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, for example, differential scanning calorimetry (DSC); x-ray powder diffraction (XRPD); and thermogravimetric analysis (TGA) to assure the crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 wt. % isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 wt. % isolated yield. Optionally, the product may be delumped by being comilled or passed through mesh screen.

The features and advantages of this disclosure may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of this disclosure that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof. The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference. All measurements are subject to experimental error and are within the spirit of the invention.

As used herein, "amorphous" refers to a solid form of a molecule and/or ion that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern with sharp maxima.

As used herein, the term "substantially pure" means the crystalline form of Compound (I) referred to contains at least about 90 wt. % based on the weight of such crystalline form. The term "at least about 90 wt. %," while not intending to limit the applicability of the doctrine of equivalents to the scope of the claims, includes, but is not limited to, for example, about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99 and about 100% wt. %, based on the weight of the crystalline form referred to. The remainder of the crystalline form of Compound (I) may comprise other Form(s) of Compound (I) and/or reaction impurities and/or processing impurities that arise, for example, when the crystalline form is prepared. The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectroscopy, and/or infrared spectroscopy.

PREPARATIVE EXAMPLES

Example 1: Preparation of N-(4-[[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof (Compound (I))

The synthetic route used for the preparation of N-(4-[[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 1:

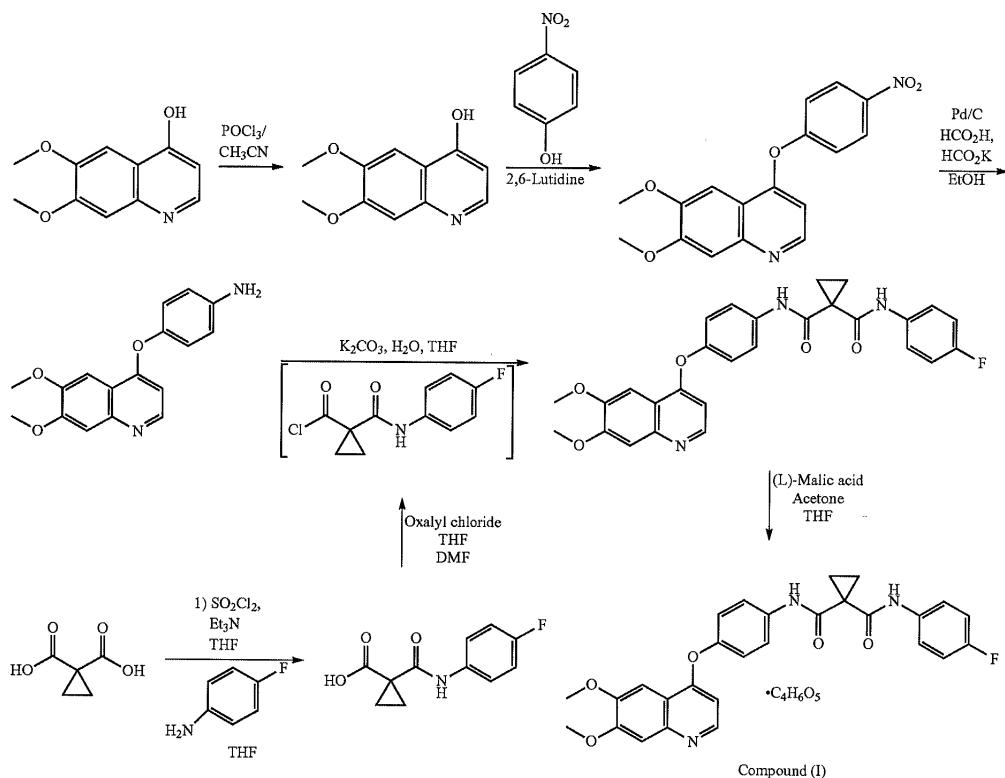
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SCHEME 1



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The process shown in Scheme 1 is described in more detail below.

1.1 Preparation of
4-Chloro-6,7-dimethoxy-quinoline

A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (1 L, 10.0 kg) and acetonitrile (64.0 L). The resulting mixture was heated to approximately 65° C. and phosphorus oxychloride (POCl_3 , 50.0 kg) was added. After the addition of POCl_3 , the temperature of the reaction mixture was raised to approximately 80° C. The reaction was deemed complete (approximately 9.0 hours) when <2% of the starting material remained (in process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 10° C. and then quenched into a chilled solution of dichloromethane (DCM, 238.0 kg), 30% NH_4OH (135.0 kg), and ice (440.0 kg). The resulting mixture was warmed to approximately 14° C., and phases were separated. The organic phase was washed with water (40.0 kg) and concentrated by vacuum distillation with the removal of solvent (approximately 190.0 kg). Methyl-t-butyl ether (MTBE, 50.0 kg) was added to the batch, and the mixture was cooled to approximately 10° C., during which time the product crystallized out. The solids

were recovered by centrifugation, washed with n-heptane (20.0 kg), and dried at approximately 40° C. to afford the title compound (8.0 kg).

45 1.2 Preparation of
6,7-Dimethyl-4-(4-nitro-phenoxy)-quinoline

A reactor was sequentially charged with 4-chloro-6,7-dimethoxy-quinoline (8.0 kg), 4 nitrophenol (7.0 kg), 4 dimethylaminopyridine (0.9 kg), and 2,6 lutidine (40.0 kg). The reactor contents were heated to approximately 147° C. When the reaction was complete (<5% starting material remaining as determined by in process HPLC analysis, approximately 20 hours), the reactor contents were allowed to cool to approximately 25° C. Methanol (26.0 kg) was added, followed by potassium carbonate (3.0 kg) dissolved in water (50.0 kg). The reactor contents were stirred for approximately 2 hours. The resulting solid precipitate was filtered, washed with water (67.0 kg), and dried at 25° C. for approximately 12 hours to afford the title compound (4.0 kg).

55 1.3 Preparation of
4-(6,7-Dimethoxy-quinoline-4-yloxy)-phenylamine

A solution containing potassium formate (5.0 kg), formic acid (3.0 kg), and water (16.0 kg) was added to a mixture of

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6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline (4.0 kg), 10% palladium on carbon (50% water wet, 0.4 kg) in tetrahydrofuran (40.0 kg) that had been heated to approximately 60° C. The addition was carried out such that the temperature of the reaction mixture remained approximately 60° C. When the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining, typically 15 hours), the reactor contents were filtered. The filtrate was concentrated by vacuum distillation at approximately 35° C. to half of its original volume, which resulted in the precipitation of the product. The product was recovered by filtration, washed with water (12.0 kg), and dried under vacuum at approximately 50° C. to afford the title compound (3.0 kg; 97% AUC).

1.4 Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid

Triethylamine (8.0 kg) was added to a cooled (approximately 4° C.) solution of commercially available cyclopropane-1,1-dicarboxylic acid (21, 10.0 kg) in THF (63.0 kg) at a rate such that the batch temperature did not exceed 10° C. The solution was stirred for approximately 30 minutes, and then thionyl chloride (9.0 kg) was added, keeping the batch temperature below 10° C. When the addition was complete, a solution of 4-fluoroaniline (9.0 kg) in THF (25.0 kg) was added at a rate such that the batch temperature did not exceed 10° C. The mixture was stirred for approximately 4 hours and then diluted with isopropyl acetate (87.0 kg). This solution was washed sequentially with aqueous sodium hydroxide (2.0 kg dissolved in 50.0 L of water), water (40.0 L), and aqueous sodium chloride (10.0 kg dissolved in 40.0 L of water). The organic solution was concentrated by vacuum distillation followed by the addition of heptane, which resulted in the precipitation of solid. The solid was recovered by centrifugation and then dried at approximately 35° C. under vacuum to afford the title compound. (10.0 kg).

1.5 Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride

Oxalyl chloride (1.0 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (2.0 kg) in a mixture of THF (11 kg) and N, N-dimethylformamide (DMF; 0.02 kg) at a rate such that the batch temperature did not exceed 30° C. This solution was used in the next step without further processing.

1.6 Preparation of N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

The solution from the previous step containing 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride was added to a mixture of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (3.0 kg) and potassium carbonate (4.0 kg) in THF (27.0 kg) and water (13.0 kg) at a rate such that the batch temperature did not exceed 30° C. When the reaction was complete (in typically 10 minutes), water (74.0 kg) was added. The mixture was stirred at 15–30° C. for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a premade solution of THF (11.0 kg) and water (24.0 kg), and dried at approximately 65° C. under vacuum for approximately 12 hours to afford the title compound (free base, 5.0 kg). ¹H NMR (400 MHz, d₆-DMSO): δ 10.2 (s,

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1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15 (m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LCMS: M+H=502.

1.7 Preparation of N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L) malate salt (Compound (I))

A solution of (L)-malic acid (2.0 kg) in water (2.0 kg) was added to a solution of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide free base (15, 5.0 kg) in ethanol, maintaining a batch temperature of approximately 25° C. Carbon (0.5 kg) and thiol silica (0.1 kg) were then added, and the resulting mixture was heated to approximately 78° C., at which point water (6.0 kg) was added. The reaction mixture was then filtered, followed by the addition of isopropanol (38.0 kg), and was allowed to cool to approximately 25° C. The product was recovered by filtration and washed with isopropanol (20.0 kg) and dried at approximately 65° C. to afford Compound (I) (5.0 kg).

Example 2: Preparation of Crystalline Compound (I), Form N-1

A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60° C. and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

At 60° C., acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60° C. for 10 hours. The solution was then cooled to 20° C. and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR; 1.20 L). The solids were dried at 60° C. (25 mm Hg) for 6 hours to afford Compound (I), Form N-1 (108 g; 0.85 equiv; 108.00 g; 85.22% yield) as a white crystalline solid.

Example 3: Alternate Preparation of Crystalline Compound (I), Form N-1

A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-[{6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 h with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

Separately, a powder blend was made with known amounts of two batches of Compound (I): (1) 300 mg of batch 1, which contained approximately 41% Compound (I), Form N-1 and 59% Compound (I), Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to Compound (I), Form N-2.

The Compound (I), Form N-1 and Compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and

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filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45° C. to afford 128 mg of crystalline Compound (I) in the N-1 form.

Example 4: Preparation of Crystalline Compound (I), Form N-2

4.1 Preparation of Crystalline Compound (I), Form N-2 Seed Crystals

A solution was prepared by combining 20 mL of acetone and 300 mg of freebase N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide in a 25 mL screw capped vial. Next, 0.758 mL of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hr at ambient temperature. The sample was then suction filtered with 0.45 μm PTFE filter cartridge and dried in vacuo at ambient temperature overnight.

4.2 Preparation of Crystalline Compound (I), Form N-2

To a reactor were added N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50° C. Seed crystals were added (1% 480 mg) and the malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 mL/min (3 h)). The slurry was held at 50° C. for 18 h and then was cooled to 25° C. over 30 min. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL.). The solids were dried under vacuum at 60° C. for 5 h to afford Compound (I) (55.7 g; 0.92 equiv; 55.70 g; 91.56% yield) as an off-white crystalline solid.

Example 5: Preparation of Crystalline Compound (III), Form N-1

A one mL aliquot (DL)-malic acid salt of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, slurried in tetrahydrofuran (THF), was heated to 60° C. on a hot-plate in a half-dram vial. Next, tetrahydrofuran was added drop-wise until an almost clear solution was obtained. The vial was capped, removed from the hot plate and equilibrated at ambient temperature without agitation. Crystallization was apparent after several hours and the solution was allowed to stand overnight to allow completion. Several droplets of the resulting slurry were placed on a glass slide for microscopic analysis. The crystalline material consisted of many elongated plates ranging up to 60 microns in the longest dimension.

Alternate Preparation of Crystalline Compound (III), Form N-1

To a reactor were added N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (15 g; 1.00 equiv; 15.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water

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content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (DL)-malic acid (1.2 equiv (molar); 4.53 g) was dissolved into methyl isobutyl ketone (8 mL/g-bulk-LR; 120.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 15.00 mL). Next, 20 mL of the solution was added to the first solution at 50° C. The malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 mL/min (3 h)). The slurry was held at 50° C. for 18 h and then was cooled to 25° C. over 30 min. The solids were filtered, and washed with 20% THF/MIBK (0V, 150 mL). The solids were dried under vacuum at 60° C. for 5 h to afford Compound (III) (15.52 g; 86.68% yield) as an off-white solid.

Example 6: Preparation of Amorphous Compound (I)

A solution was prepared with 5 g of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N^t-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate and 250 mL of a 1:1 (v:v) mixture of methanol and dichloromethane. The hazy solution was filtered through a 0.45 micron filter to yield a clear, yellowish solution. The solution was pumped through the spray dryer nozzle at a rate of 12.9 cc/min, and was atomized by nitrogen gas fed at a rate of 10.911 min. The temperature at the inlet of the cyclone was set to 65° C. to dry the wet droplets. Dry amorphous powder (1.5 g) was collected (yield=30%).

CHARACTERIZATION EXAMPLES

I. NMR Spectra in Dimethyl Sulfoxide Solution

1.1 Compound (I), Form N-1

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, 1H, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91,

99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17,

122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7,

149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07,

171.83, 174.68.

1.2 Compound (I), Form N-2

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91,

99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17,

122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7,

149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07,

171.83, 174.68.

1.3 Compound (III), Form N-1

¹H NMR (400 MHz, d₆-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

¹³C NMR (d₆-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91,

99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17,

122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7,

149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07,

171.83, 174.68.

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122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

Characterization of Solid State Forms of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate

II. Powder X-Ray Diffraction (XRPD) Studies

X-Ray Powder Diffraction (XRPD) patterns were collected on a Bruker AXS C2 GADDS diffractometer equipped with an automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. The radiation source used was copper ($\text{Cu K}\alpha=1.5406 \text{ \AA}$), wherein the voltage was set at 40 kV and the current was set at 40 mA, X-ray optics consists of a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm. The beam divergence, i.e. the effective size of the X-ray beam on the sample, was approximately 4 mm. A $\theta\text{-}\theta$ continuous scan mode was employed with a sample-detector distance of 20 cm which gives an effective 20 range of 3.2°-29.8°. Samples run under ambient conditions (from about 18° C. to about 25° C.) were prepared as flat plate specimens using powder as received without grinding. Approximately 1.2 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. Typically the sample would be exposed to the X-ray beam for 120 seconds. Beam divergence (i.e., effective size of X-ray spot, gives a value of approximately 4 mm. Alternatively, the powder samples were placed in sealed glass capillaries of 1 mm or less in diameter; the capillary was rotated during data collection at a sample-detector distance of 15 cm. Data were collected for $3^\circ \leq 2\theta \leq 35^\circ$ with a sample exposure time of at least 2000 seconds. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional XRPD pattern with a step size of 0.02 °20 in the range of 3 to $35^\circ 20 \pm 0.2^\circ 20$. The software used for data collection was GADDS for WNT 4.1.16 and the data were analyzed and presented using Diffrac Plus EVA v 9.0.0.2 or v 13.0.0.2.

II.1 Compound (I), Form N-1

FIG. 1 shows the experimental XRPD pattern of crystalline Compound (I), Form N-1 acquired at room temperature (about 25° C.). A list of the peaks are shown in Table 2, above. The 2θ values at 19.4, 21.5, 22.8, 25.1, and 27.6 ($\pm 0.2^\circ 20$) are useful for characterizing crystalline Compound (I), Form N-1. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

II.2 Compound (I), Form N-2

FIG. 8 shows the experimental XRPD pattern of crystalline Compound (I), Form N-2 acquired at room temperature (about 25° C.). A list of the peaks are shown in Table 2, above. The 2θ values at 20.9 and 21.9 ($\pm 0.2^\circ 20$) are useful for characterizing crystalline Compound (I), Form N-2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

II.3 Compound (III), Form N-1

FIG. 15 shows the experimental and the simulated XRPD pattern of crystalline Compound (III), Form N-1, acquired at 25° C. using a spinning capillary sample. A list of the peaks are shown in Table 2, above. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-2.

II.4 Amorphous Compound (I)

FIG. 22 shows the experimental XRPD pattern of amorphous Compound (I) acquired at room temperature (about

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25° C.). The spectra is characterized a broad peak and the absence of sharp peaks, which is consistent with an amorphous material.

III. Single Crystal X-Ray Study for Compound (III), Form N-1

Data were collected on a Bruker-Nonius CAD4 serial diffractometer. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Intensities were measured using Cu K α radiation ($\lambda=1.5418 \text{ \AA}$) at a constant temperature with the $\theta\text{-}2\theta$ variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Alternately, single crystal data were collected on a Bruker-Nonius Kappa CCD 2000 system using Cu K α radiation ($\lambda=1.5418 \text{ \AA}$). Indexing and processing of the measured intensity data were carried out with the HKL2000 software package (Otwinowski, Z. & Minor, W. (1997) in *Macromolecular Crystallography*, eds. Carter, W. C. Jr & Sweet, R. M. (Academic, NY), Vol. 276, pp. 307-326) in the Collect program suite (Collect Data collection and processing user interface: Collect. Data collection software, R. Hooft, Nonius B. V., 1998). Alternately, single crystal data were collected on a Bruker-AXS APEX2 CCD system using Cu K α radiation ($\lambda=1.5418 \text{ \AA}$). Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27). When indicated, crystals were cooled in the cold stream of an Oxford cryo system (Oxford Cryosystems Cryostream cooler J. Cosier and A. M. Glazer, *J. Appl. Cryst.*, 1986, 19, 105) during data collection.

The structures were solved by direct methods and refined on the basis of observed reflections using either the SDP software package (SDP, Structure Determination Package, Enraf-Nonius, Bohemia N.Y. 11716. Scattering factors, including f and f', in the SDP software were taken from the "International Tables for Crystallography", Kynoch Press, Birmingham, England, 1974; Vol IV, Tables 2.2A and 2.3.1) with minor local modifications or the crystallographic packages MAXUS (maXus solution and refinement software suite: S. Mackay, C. J. Gilmore, C. Edwards, M. Tremayne, N. Stewart, K. Shankland. maXus: a computer program for the solution and refinement of crystal structures from diffraction data) or SHELXTL (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27).

The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. The function minimized in the refinements was $\Sigma_w (|F_o| - |F_c|)^2$. R is defined as $\Sigma |F_o| - |F_c| / \Sigma |F_o|$ while $R_{wR} = [\Sigma_w (|F_o| - |F_c|)^2 / \Sigma_w |F_o|^2]^{1/2}$ where w is an appropriate weighting function based on errors in the observed intensities. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors, but no hydrogen parameters were varied.

"Hybrid" simulated powder X-ray patterns were generated as described in the literature (Yin, S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougeoutas, J. Z., *American Pharmaceutical Review*, 2003, 6, 2, 80). The room temperature cell parameters were obtained by performing a cell refinement using the CellRefine.xls program. Input to the program includes the 2-theta position of ca. 10 reflections, obtained from the experimental room temperature powder pattern; the corresponding Miller indices, hkl, were assigned based on the single-crystal data collected at low temperature. A new (hybrid) XRPD was calculated (by either of the software programs, Alex or LatticeView) by inserting the

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molecular structure determined at low temperature into the room temperature cell obtained in the first step of the procedure. The molecules are inserted in a manner that retains the size and shape of the molecule and the position of the molecules with respect to the cell origin, but, allows intermolecular distances to expand with the cell.

A single crystal, measuring 40x30x10 microns, was selected from the slurry of crystals described in Example 5 for single crystal diffraction analysis. The selected crystal was affixed to a thin glass fiber with a small amount of a light grease, and mounted at room temperature on a Bruker ApexII single crystal diffractometer equipped with a rotating copper anode.

Crystalline Compound (III), From N-1 is characterized by unit cell parameters approximately equal to those reported in Table 4. The unit cell parameters were measured at a temperature of about 25° C.

TABLE 4

a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°
Space group: P2 ₁ /n
Molecules of Compound (I)/unit cell: 4
Volume = 2969 Å ³

Structure solution and refinement were routine in the monoclinic space group, P2₁/n, with four formula units in the unit cell. The structure contains cations of N-(4-[6,7-bis(methoxy)-quinolin-4-yl]oxy)phenyl-N¹-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, protonated at the quinoline nitrogen atom, and singly ionized malic acid anions, in a 1:1 ratio. Further, the crystal contained a 1:1 ratio of (L)-malic acid ions to (D)-malic acid ions. Table 5 fractional atomic coordinates for Compound (III), Form N-1 calculated at a temperature of about 25° C.

Based on the single crystal X-ray data, crystalline Compound (III), Form N-1 may be characterized by a simulated powder x-ray diffraction (XRPD) pattern substantially in accordance with the simulated pattern shown in FIG. 15 and/or an observed XRPD pattern substantially in accordance with the experimental pattern shown in FIG. 15.

TABLE 5

Fractional Atomic Coordinates for Compound (III), Form N-1
Calculated at a Temperature of about 25° C.

Atom	X	Y	Z
O1	0.30601	-0.52166	0.22875
O2	0.29518	0.12504	0.09391
O3	0.19041	-0.53232	0.18147
F5	-0.07307	2.12170	-0.08811
O6	0.18186	1.20500	-0.03241
O7	0.57137	0.22739	0.23473
O8	0.58700	-0.17911	0.24998
O9	0.41742	0.76377	-0.04319
N10	0.28649	0.82210	-0.01420
O11	0.87391	0.22086	0.31241
N12	0.46887	0.17029	0.17613
C13	0.29647	0.64886	0.01247
C14	0.31416	1.08187	-0.06304
C15	0.33900	-0.02207	0.14761
N16	0.20651	1.40640	-0.08267
C17	0.40079	-0.01723	0.17602
C18	0.29743	0.29956	0.06604
C19	0.00418	1.80556	-0.05680

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TABLE 5-continued

Fractional Atomic Coordinates for Compound (III), Form N-1 Calculated at a Temperature of about 25° C.				
5	Atom	X	Y	Z
C20	0.11925	1.73626	-0.11097	
C21	0.22556	1.24019	-0.05791	
C22	0.39150	-0.17467	0.20389	
C23	0.22558	0.63870	0.03619	
10	O24	0.62714	0.39565	0.29760
C25	0.34591	0.87438	-0.03961	
C26	0.36467	-0.51389	0.25773	
C27	0.26562	-0.20277	0.14859	
C28	0.35380	0.15272	0.12054	
C29	0.07365	1.60604	-0.05443	
15	C30	0.04897	1.92890	-0.11212
C31	0.73841	0.04517	0.28641	
C32	0.32089	-0.35160	0.20385	
C33	0.36641	0.29052	0.04302	
C34	0.42458	0.32272	0.12143	
C35	0.11723	-0.54030	0.15742	
20	C36	0.12933	1.59042	-0.08228
C37	-0.00344	1.93494	-0.08547	
C38	0.36439	0.47245	0.01586	
C39	0.59040	0.05797	0.25625	
C40	0.25712	-0.35516	0.17574	
C41	0.63543	0.13842	0.29041	
C42	0.22703	0.46640	0.06306	
25	C43	0.34559	1.01717	-0.10021
C44	0.39312	1.20834	-0.08137	
C45	0.48224	0.32340	0.15059	
O46	0.77400	0.04784	0.34652	
C47	0.79349	0.09920	0.31966	
H10	0.22646	0.91057	-0.01479	
30	H16	0.24790	1.42164	-0.10317
H19	-0.04176	1.82973	-0.03893	
H20	0.16347	1.73025	-0.13083	
H22	0.43179	-0.17902	0.22447	
H23	0.17093	0.73524	0.03244	
H27	0.21953	-0.24212	0.12962	
35	H29	0.07954	1.50390	-0.03492
H30	0.04671	2.05817	-0.13354	
H33	0.41851	0.16255	0.04395	
H34	0.43433	0.41859	0.10106	
H38	0.41440	0.45648	-0.00227	
H41	0.61062	0.02238	0.31086	
H42	0.17752	0.45794	0.07911	
40	H45	0.53033	0.44239	0.15049
H31a	0.76754	0.12071	0.26693	
H31b	0.74726	-0.15247	0.28137	
H43a	0.30237	1.06909	-0.12187	
H43b	0.36868	0.85693	-0.10836	
H44a	0.45563	1.18725	-0.07495	
45	H44b	0.38932	1.39942	-0.08846
H26a	0.35958	-0.37184	0.27147	
H26b	0.42813	-0.55605	0.25348	
H26c	0.34954	-0.66814	0.27571	
H35a	0.08189	-0.39941	0.15398	
50	H35b	0.06671	-0.68838	0.16269
H35c	0.13276	-0.61095	0.13323	
H11	0.88836	0.21926	0.28968	
H12	0.50720	0.16494	0.19477	
H24	0.61522	0.45898	0.27789	

IV. Solid State Nuclear Magnetic Resonance (SSNMR)

All solid-state C-13 NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and the TPPM pulse sequence and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A. E. Bennett et al, *J. Chem. Phys.*, 1995, 103, 6951), (G. Metz, X. Wu and S. O. Smith, *J. Magn. Reson. A*, 1994, 110, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance being set to 38.56 ppm (W. L Earl and D. L VanderHart, *J. Magn. Reson.*, 1982, 48, 35-54).

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IV.1 Compound (I), Form N-1

The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-1 is shown in FIG. 2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

SS ^{13}C NMR Peaks: 18.1, 20.6, 26.0, 42.9, 44.5, 54.4, 55.4, 56.1, 70.4, 99.4, 100.1, 100.6, 114.4, 114.9, 115.8, 119.6, 120.1, 121.6, 123.2, 124.1, 136.4, 138.6, 140.6, 145.4, 150.1, 150.9, 156.2, 157.4, 159.4, 164.9, 167.1, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm.

FIG. 3 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

FIG. 4 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows a peak at -121.6, -120.8, and -118.0 ppm, ± 0.2 ppm.

IV.2 Compound (I), Form N-2

The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-2 is shown in FIG. 9. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

SS ^{13}C NMR Peaks: 20.5, 21.8, 23.0, 25.9, 26.4, 38.0, 41.7, 54.7, 55.8, 56.2, 56.6, 69.7, 99.4, 100.0, 100.4, 100.8, 102.3, 114.5, 115.5, 116.7, 119.0, 120.2, 121.1, 121.2, 122.1, 122.9, 124.5, 136.0, 137.3, 138.1, 138.9, 139.5, 140.2, 144.9, 145.7, 146.1, 150.7, 156.7, 157.7, 159.6, 159.7, 165.1, 167.0, 168.0, 171.5, 177.3, 179.3, 180.0, and 180.3 ppm, ± 0.2 ppm.

FIG. 10 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

FIG. 11 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at -121.0 and -119.1 ppm, ± 0.2 ppm. Those peaks, individually or together, may be sufficient to characterize crystalline Compound (I), Form N-2.

IV.3 Compound (III), Form N-1

The solid state ^{13}C NMR spectrum of crystalline Compound (III), Form N-1 is shown in FIG. 16. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

SS ^{13}C NMR Peaks: 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, and 182.1 ppm, ± 0.2 ppm.

FIG. 17 shows the solid state ^{15}N NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows peaks at 119.6, 134.7, and 175.5 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

FIG. 18 shows the solid state ^{19}F NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows a peak at -120.5 ppm, ± 0.2 ppm.

IV.4 Compound (I), Amorphous

FIG. 23 shows the solid state ^{13}C NMR spectrum of amorphous Compound (I). The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

SS ^{13}C NMR Peaks (ppm): 12.2, 17.8, 20.3, 21.8, 27.2, 33.8, 41.7, 56.9, 69.9, 99.9, 102.2, 115.6, 122.2, 134.4,

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137.8, 142.9, 149.1, 150.9, 157.3, 159.7, 167.0, 171.7, 173.1, 177.4, and 179.5 ppm, ± 0.2 ppm.

FIG. 24 shows the solid state ^{15}N NMR spectrum of amorphous Compound (I). The spectrum shows peaks at 120.8, 131.8, 174.7, and 178.3 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

FIG. 25 shows the solid state ^{19}F NMR spectrum of amorphous Compound (I). The spectrum shows a peak at -118.9 ppm, ± 0.2 ppm.

V. Thermal Characterization Measurements
Thermal Gravimetric Analysis (TGA)

The TGA measurements were performed in a TA InstrumentsTM model Q500 or 2950, employing an open pan setup. The sample (about 10-30 mg) was placed in a platinum pan previously tared. The weight of the sample was measured accurately and recorded to a thousand of a milligram by the instrument. The furnace was purged with nitrogen gas at 100 mL/min. Data were collected between room temperature and 300° C. at 10° C./min heating rate.

Differential Scanning Calorimetry (DSC) Analysis

DSC measurements were performed in a TA InstrumentsTM model Q2000, Q1000 or 2920, employing an open pan setup. The sample (about 2-6 mg) was weighed in an aluminum pan and recorded accurately recorded to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50 mL/min. Data were collected between room temperature and 300° C. at 10° C./min heating rate. The plot was made with the endothermic peaks pointing down.

V.1 Compound (I), Form N-1

FIG. 5 shows the TGA thermogram for crystalline Compound (I), Form N-1, which shows a weight loss of approximately 0.4 weight % at a temperature of 170° C.

FIG. 6 shows the DSC thermogram for crystalline Compound (I), Form N-1, which showed a melting point of approximately 187° C.

V.2 Compound (I), Form N-2

FIG. 12 shows the TGA thermogram for crystalline Compound (I), Form N-2, which shows a weight loss of approximately 0.1 weight % at a temperature of 170° C.

FIG. 13 shows the DSC thermogram for crystalline Compound (I), Form N-2, which showed a melting point of approximately 186° C.

V.3 Compound (III), Form N-1

FIG. 19 shows the TGA thermogram for crystalline Compound (III), Form N-1, which shows a weight loss of approximately 0.2 weight % at a temperature of 170° C.

FIG. 20 shows the DSC thermogram for crystalline Compound (III), Form N-1, which showed a melting point of approximately 186° C.

V.2 Compound (I), Amorphous

FIG. 26 shows the DSC for crystalline Compound (I).

VI. Moisture Vapor Isotherm Measurements

Moisture sorption isotherms were collected in a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was dried at 60° C. until the loss rate of 0.0005 wt %/min was obtained for 10 minutes. The sample was tested at 25° C. and 3 or 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95% RH. Equilibration at each RH was reached when the rate of 0.0003 wt %/min for 35 minutes was achieved or a maximum of 600 minutes.

VI.1 Compound (I), Form N-1

FIG. 7 shows the moisture vapor isotherm of crystalline Compound (I), Form N-1.

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VI.2 Compound (I), Form N-1

FIG. 14 shows the moisture vapor isotherm of crystalline Compound (I), Form N-2.

VI.3 Compound (III), Form N-1

FIG. 21 shows the moisture vapor isotherm of crystalline Compound (III), Form N-1.

VI.4 Compound (I), Amorphous

FIG. 27 shows the moisture vapor isotherm of amorphous Compound (I).

The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following

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appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methoxy)quino-
lin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-
1,1-dicarboxamide, malate salt, wherein said salt is the
15 (L)-malate salt or the (D)-malate salt, and wherein said salt
is crystalline.

2. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methoxy)qui-
nolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-
1,1-dicarboxamide, malate salt, wherein said salt is the
20 (L)-malate salt or the (D)-malate salt, said salt is crystalline,
and said cancer is kidney cancer.

3. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methoxy)qui-
nolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-
1,1-dicarboxamide, malate salt, wherein said salt is the
25 (L)-malate salt or the (D)-malate salt, said salt is crystalline,
and said cancer is liver cancer.

* * * * *

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**CERTIFICATE OF COMPLIANCE
WITH TYPE-VOLUME LIMITATIONS**

The foregoing filing complies with the relevant type-volume limitation of the Federal Rules of Appellate Procedure and Federal Circuit Rules because the filing has been prepared using a proportionally spaced typeface and includes 13,977 words.

/s/ Bryce A. Cooper
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